EDITORIAL

The Yin and Yang of Perioperative Medicine

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The past four decades have seen remarkable progress in establishing best perioperative practices.[1] One of the challenges in improving perioperative care, however, is rooted in the interplay of the myriad interdependent, often opposing, mechanisms that contribute to perioperative myocardial infarction — excess bleeding, dramatic fluid shifts, unrelenting tachycardia, myocardial stress with fixed coronary obstruction, profound hypotension or hypertension, coronary plaque rupture, and coronary spasm. Strategies that mitigate one mechanism may lead to another. Devereaux et al. now report on two such strategies in the *Journal* — the perioperative use of aspirin and the perioperative use of clonidine in patients undergoing noncardiac surgery.[2,3]

The authors report the results of the Perioperative Ischemic Evaluation 2 (POISE-2) trial, which was designed to evaluate separately the efficacy and safety of low-dose clonidine versus placebo and low-dose aspirin versus placebo in 10,010 patients with, or at risk for, atherosclerotic disease. Both in patients who had not been taking aspirin before the study and in those who were already on an aspirin regimen (the latter referred to as the continuation stratum), aspirin had no significant effect on the composite primary end point of death or nonfatal myocardial infarction at 30 days. Major bleeding was more common in the aspirin group than in the placebo group (4.6% vs. 3.7%; hazard ratio, 1.23; 95% confidence interval [CI], 1.01 to 1.49; P=0.04). Overall, it is likely that aspirin prevented some perioperative myocardial infarctions through thrombus inhibition, but this may have been at the expense of bleeding and other myocardial infarctions induced by a mismatch between the supply of and demand for oxygen. It would be important to investigate the temporal relationship between major bleeding and myocardial infarction. Importantly, among 4382 patients in the continuation stratum, there was no "rebound" increase in thrombotic events due to temporary perioperative interruption of aspirin. All the findings applied regardless of whether patients had a history of vascular disease or no history of vascular disease.

On balance, the authors provide cogent evidence against the use of aspirin perioperatively in patients with and those without preexisting vascular disease. Nonetheless, important questions linger. Although a substantial proportion of patients in the POISE-2 trial had some form of vascular disease, only 4.3% of the patients in the aspirin group had undergone prior coronary stenting. The safety of aspirin withdrawal in those who have previously undergone percutaneous coronary interventions may not be established by the POISE-2 trial. Furthermore, the authors excluded patients who had received a bare-metal or drug-eluting coronary stent less than 6 weeks and less than 1 year, respectively, before surgery. Perioperative aspirin may prevent myocardial infarction and stent thrombosis in patients with recent percutaneous coronary interventions and should not be withdrawn prematurely.[4]

The use of low-dose clonidine, which blunts sympathetic outflow, would seem to be a beneficial addition to the armamentarium of the perioperative clinician. In the POISE-2 trial, however, clonidine did not significantly reduce the risk of the primary outcome and, as compared with placebo, was associated with higher rates of clinically important hypotension (47.6% vs. 37.1%; hazard ratio, 1.32; 95% CI, 1.24 to 1.40; P<0.001)

and nonfatal cardiac arrest (0.3% vs. 0.1%; hazard ratio, 3.20; 95% CI, 1.17 to 8.73; P=0.02). Given these harms and the neutral effect on the primary outcome, clonidine should be avoided perioperatively. The prevalence of clinically important hypotension in both the clonidine group and the placebo group, however, bears scrutiny and could reflect the intensity of monitoring in the POISE-2 trial. Although one could even question the relevance of the results of the aspirin study in a trial in which so many patients had clinically important hypotension (which was an independent predictor of subsequent myocardial infarction), the authors report that there was no significant effect of clonidine on the results of the comparison of aspirin with placebo. Furthermore, the effect of metoprolol succinate in the POISE trial[5] in reducing the risk of myocardial infarction is contradictory to the deleterious effect of clonidine in the POISE-2 trial. Although the blunting of sympathetic outflow produced by clonidine may be fundamentally different from that produced by beta-blockers, the results of the POISE and POISE-2 trials taken together offer credibility to a calculated strategy of decreasing heart rate while avoiding perioperative hypotension.

The perioperative medicine community welcomes the results of the POISE-2 trial, while realizing that there are still many areas of uncertainty, including best practice in those who have undergone any percutaneous coronary intervention. It is not surprising that medical therapies directed at favorably modifying one mechanism causing perioperative myocardial infarction have the potential to increase risk through augmentation of a different pathway. Aspirin may reduce coronary thrombosis at the expense of excess bleeding; clonidine may reduce hypertensive swings only to be countered by clinically important hypotension. As observed by Chinese philosophers, the whole is made up of the yin and yang — complementary, interdependent, and conceptually opposing entities that comprise a whole. Future progress in perioperative medicine may depend on the implementation of strategies that successfully address one pathophysiological mechanism of perioperative myocardial infarction without being limited by another.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Aspirin in Patients Undergoing Noncardiac Surgery

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ABSTRACT

BACKGROUND

There is substantial variability in the perioperative administration of aspirin in patients undergoing noncardiac surgery, both among patients who are already on an aspirin regimen and among those who are not.

METHODS

Using a 2-by-2 factorial trial design, we randomly assigned 10,010 patients who were preparing to undergo noncardiac surgery and were at risk for vascular complications to receive aspirin or placebo and clonidine or placebo. The results of the aspirin trial are reported here. The patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, with 5628 patients) or they were already on an aspirin regimen (continuation stratum, with 4382 patients). Patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days.

RESULTS

The primary outcome occurred in 351 of 4998 patients (7.0%) in the aspirin group and in 355 of 5012 patients (7.1%) in the placebo group (hazard ratio in the aspirin group, 0.99; 95% confidence interval [CI], 0.86 to 1.15; P=0.92). Major bleeding was more common in the aspirin group than in the placebo group (230 patients [4.6%] vs. 188 patients [3.8%]; hazard ratio, 1.23; 95% CI, 1.01, to 1.49; P=0.04). The primary and secondary outcome results were similar in the two aspirin strata.

CONCLUSIONS

Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. (Funded by the Canadian Institutes of Health Research and others; POISE-2 ClinicalTrials.gov number, NCT01082874.)

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Myocardial infarction is the most common major vascular complication that occurs after noncardiac surgery.[1-3] Noncardiac surgery is associated with platelet activation,[4] and coronary-artery thrombus may be a mechanism of perioperative myocardial infarction.[5,6] Aspirin inhibits platelet aggregation,[7] and the perioperative administration of aspirin may prevent major vascular complications by inhibiting thrombus formation.[8]

In a meta-analysis of data from large, randomized trials involving more than 110,000 patients who were not undergoing surgery, the use of aspirin was shown to prevent myocardial infarction and major vascular events.[9] High-dose aspirin has not been shown to be superior to low-dose aspirin in preventing vascular complications,[10,11] and low-dose aspirin has been associated with a lower incidence of gastric toxic effects.[12]

Although there is strong evidence that aspirin prevents venous thromboembolism after noncardiac surgery,[13,14] physicians more commonly use anticoagulant therapy for the prevention of venous thromboembolism.[15] Nevertheless, one third of patients undergoing noncardiac surgery who are at risk for major vascular complications receive perioperative aspirin.[16] Among patients undergoing noncardiac surgery, there is variability in the use of perioperative aspirin both among patients who are not already taking aspirin and among those who are on long-term aspirin regimens.[17] Uncertainty regarding the risks and benefits of aspirin underscores the need for a large perioperative trial.[18,19]

We conducted the Perioperative Ischemic Evaluation 2 (POISE-2) trial to evaluate the effect of low-dose aspirin, as compared with placebo, on the 30-day risk of a composite of death or nonfatal myocardial infarction among patients who were undergoing noncardiac surgery.

METHODS

STUDY DESIGN

POISE-2 was an international, randomized, controlled trial with a 2-by-2 factorial design to separately evaluate the effects of aspirin versus placebo (reported here) and clonidine versus placebo (reported elsewhere in the *Journal*)[20] in patients undergoing noncardiac surgery. Details of the trial objectives, design, and methods have been reported previously.[21] All centers obtained ethics approval before starting recruitment.

STUDY OVERSIGHT

The study was funded by the Canadian Institutes of Health Research and others. The Population Health Research Institute was the study coordinating center and was responsible for the randomization design, maintenance of the database, data validation, analyses, and study-center coordination. Bayer Pharma provided the aspirin used in the study, and Boehringer Ingelheim provided the clonidine and some research funding; both companies were provided with the first draft of the manuscript. However, no donor or funder had a role in the design or conduct of the study, the collection or analyses of the data, or the preparation of the manuscript. The operations committee designed the trial, prespecified the statistical analysis plan, and vouches for the completeness and accuracy of the data and analyses and the adherence of the study to the protocol (available with the full text of this article at NEJM.org). The first author wrote the first draft of the manuscript, and the writing committee made revisions and made the decision to submit the manuscript for publication.

PATIENTS

We recruited patients from July 2010 through December 2013 at 135 hospitals in 23 countries. Eligibility criteria are reported in Section 1 in the Supplementary Appendix, available at NEJM.org. Patients were then stratified according to whether they were not taking aspirin before study enrollment (initiation stratum) or they were already on an aspirin regimen (which was defined as daily use for at least 1 month within 6 weeks before surgery) (continuation stratum). Patients in the continuation stratum were required to stop taking aspirin at least 3 days before surgery to participate in the trial.

PROCEDURES

After providing written informed consent before surgery, patients underwent randomization by means of a 24-hour computerized Internet system that used block randomization stratified according to study center and aspirin stratum. Patients were assigned in a 1:1:1:1 ratio to receive aspirin and clonidine, aspirin placebo and clonidine, aspirin and clonidine placebo, or aspirin placebo and clonidine placebo. Patients, clinicians, data collectors, and outcome adjudicators were all unaware of study-group assignments.

Patients started taking aspirin or placebo (at

a dose of 200 mg) just before surgery and continued it (at a dose of 100 mg per day) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. Patients also started clonidine (0.2 mg per day) or placebo just before surgery and continued it for 72 hours. If a patient had life-threatening or major bleeding, the aspirin study drug was to be stopped. (Details regarding the follow-up process are provided in Section 2 in the Supplementary Appendix.)

STUDY OUTCOMES

The primary outcome was a composite of death or nonfatal myocardial infarction 30 days after randomization. Details regarding the two secondary composite outcomes, the tertiary outcomes, and the safety outcomes at 30 days are provided in Section 3 in the Supplementary Appendix, outcome definitions are provided in Section 4 in the Supplementary Appendix, and events evaluated by outcome adjudicators, which were used in the analyses, are provided in Section 5 in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that enrollment of 10,000 patients would give the study a power of 84% to detect a hazard ratio of 0.75 in the aspirin group, at a two-sided alpha level of 0.05, on the assumption that the rate of the primary outcome in the placebo group would be 6.1%.[16] An external data and safety monitoring committee reviewed the data when 25%, 50%, and 75% of the 30-day data were available.

We evaluated patients according to the group to which they were assigned, censoring the data for patients who were lost to follow-up on the last day that their status was known. Outcomes were analyzed with the use of Cox proportional-hazards models, stratified according to the aspirin stratum and status with respect to receipt of clonidine, except for the outcome of acute kidney injury with receipt of dialysis, for which we used logistic-regression analysis, and outcomes with respect to the length of the hospital stay, for which we used the log-rank test.

For the primary outcome, we performed subgroup analyses that were based on the aspirin stratum, type of surgery (vascular vs. nonvascular), and the number of criteria of the Revised Cardiac Risk Index that the patient met.[22] We also performed subgroup analyses, according to the aspirin stratum, for one of the secondary composite outcomes and for the tertiary outcomes. In a prespecified analysis, we predicted the direction of potential subgroup effects. For the subgroup analyses, we used Cox proportional-hazards models that incorporated tests of interaction, with a P value of less than 0.05 indicating statistical significance. All analyses were performed with the use of SAS software, version 9.1.

RESULTS

PATIENTS

A total of 10,010 patients were enrolled (5628 in the initiation stratum and 4382 in the continuation stratum). Of these patients, 4998 were assigned to receive aspirin and 5012 to receive placebo. The 30-day follow-up was complete for 99.9% of the patients (Fig. S1 in the Supplementary Appendix).

The baseline characteristics were similar in the aspirin and placebo groups (Table 1). The mean age was 68.6 years; 52.8% of the patients were men, 32.7% had a history of vascular disease, and 4.3% had undergone previous coronary stenting. Among patients in the continuation stratum, aspirin was stopped a median of 7 days (interquartile range, 4 to 8) before surgery. In the first 3 days after surgery, 65.0% of the patients received prophylactic anticoagulation. Overall, 80.4% of the patients in the aspirin group and 82.4% of those in the placebo group took at least 80% of the doses of the study drug (Table S1 in the Supplementary Appendix).

STUDY OUTCOMES

The primary outcome (death or nonfatal myocardial infarction) occurred in 351 of 4998 patients (7.0%) in the aspirin group and in 355 of 5012 patients (7.1%) in the placebo group (hazard ratio in the aspirin group, 0.99; 95% confidence interval [CI], 0.86 to 1.15; P=0.92) (Table 2 and Fig. 1). The use of aspirin did not significantly affect the secondary composite or tertiary outcomes. Myocardial infarction occurred in 309 patients (6.2%) in the aspirin group and in 315 patients (6.3%) in the placebo group (hazard ratio, 0.98; 95% CI, 0.84 to 1.15; P=0.85). Aspirin increased the risk of major bleeding, as compared with placebo, with major bleeding occurring in 230 patients (4.6%) versus 188 patients (3.8%) (hazard ratio, 1.23; 95% CI, 1.01 to 1.49; P=0.04) (Table 2, and Fig. S2 in the Supplementary Appendix). The most common sites of bleeding were the surgical

Our decision to allow patients to participate in the Continuation Stratum even if they have taken their ASA no less than 72 hours prior to surgery was based upon the following 2 considerations. First, the mean life span of human platelets is approximately 8 to 10 days, and about 12% of circulating platelets are replaced every 24 hours.35, 36 O'Brien36 demonstrated that abnormal platelet aggregation after ingestion of ASA can be corrected ex vivo by 10% normal platelet-rich plasma. Furthermore, it has been reported that if as little as 20% of platelets have normal COX-1 activity, hemostasis is unimpaired.37, 38 Therefore, stopping ASA for 72 hours is likely to ensure substantial (if not complete) recovery of platelet function. Second, investigators of the ISIS-2 trial that randomized 17,187 patients to ASA or placebo in the acute myocardial infarction setting included patients who were taking ASA chronically even if they took ASA on the day of their myocardial infarction.34 There were 2,266 patients in this subgroup, and ASA demonstrated a statistically significant reduction in vascular death, consistent with the overall finding

site (78.3%) and gastrointestinal tract (9.3%). Stroke occurred in 16 patients (0.3%) in the aspirin group and in 19 patients (0.4%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.43 to 1.64; P=0.62). The median length of hospital stay was 4 days (interquartile range, 3 to 7) in both the aspirin and placebo groups (P=0.79). There was no significant difference between the study groups in the length of stay in the intensive care unit or cardiac care unit (P=0.23). There was no significant effect of clonidine on the results comparing aspirin with placebo (P≥0.12 for all interactions).

The effect of aspirin was consistent across subgroups (P≥0.16 for all interactions) (Fig. 2). The subgroup analysis of the secondary composite outcome also showed no significant heterogeneity (P=0.72 for interaction).

DIFFERENCES BETWEEN STRATA

Aspirin use significantly increased the risk of major bleeding and decreased the risk of stroke in the initiation stratum (P=0.03 for both comparisons) and significantly increased the rate of acute kidney injury requiring dialysis in the continuation stratum (P=0.04) (Tables S2 and S3 in the Supplementary Appendix). However, the P value for strata interaction was significant only for stroke (P=0.01) (Table S4 in the Supplementary

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Aspirin (N=4998)	Placebo (N=5012)
Age — yr	68.6±10.3	68.6±10.3
Male sex — no. (%)	2597 (52.0)	2686 (53.6)
Eligibility criteria met — no. (%)		
History of vascular disease	1636 (32.7)	1635 (32.6)
Coronary artery disease	1153 (23.1)	1115 (22.2)
Peripheral arterial disease	438 (8.8)	427 (8.5)
Stroke	250 (5.0)	292 (5.8)
Undergoing major vascular surgery	244 (4.9)	245 (4.9)
Risk criteria†	4161 (83.3)	4139 (82.6)
Undergoing major surgery‡	3906 (78.2)	3896 (77.7)
Requiring emergency surgery	357 (7.1)	366 (7.3)
Age ≥70 yr	2638 (52.8)	2603 (51.9)
Diabetes requiring medication	1874 (37.5)	1911 (38.1)
Preoperative serum creatinine >2.0 mg/dl (175 μmol/liter)	164 (3.3)	156 (3.1)
History of congestive heart failure	183 (3.7)	154 (3.1)
History of transient ischemic attack	181 (3.6)	182 (3.6)
History of hypertension	4280 (85.6)	4355 (86.9)
History of smoking within 2 yr before surgery	1295 (25.9)	1262 (25.2)
Other medical history — no. (%)		
History of coronary-artery bypass grafting	241 (4.8)	240 (4.8)
History of percutaneous coronary intervention	234 (4.7)	236 (4.7)
Bare-metal stent	128 (2.6)	127 (2.5)
Drug-eluting stent	54 (1.1)	65 (1.3)
Unknown stent type	29 (0.6)	24 (0.5)
No stent	22 (0.4)	19 (0.4)
Missing data	1 (<0.1)	1 (<0.1)
Dialysis in week before randomization	69 (1.4)	58 (1.2)
Median preoperative hemoglobin (IQR) — g/liter	133 (121–144)	133 (120–144)
Time from randomization to surgery — no. (%)		
≤24 hr	4777 (95.6)	4795 (95.7)
>24–48 hr	45 (0.9)	49 (1.0)
≥48 hr	176 (3.5)	168 (3.4)

Table 1. (Continued.)

Characteristic	Aspirin (N=4998)	Placebo (N=5012)
Surgery — no./total no. (%)§		
Any procedure	4953/4998 (99.1)	4979/5012 (99.3)
Orthopedic	1891/4953 (38.2)	1953/4979 (39.2)
General	1327/4953 (26.8)	1337/4979 (26.9)
Urologic or gynecologic	827/4953 (16.7)	835/4979 (16.8)
Vascular	309/4953 (6.2)	296/4979 (5.9)
Thoracic	293/4953 (5.9)	298/4979 (6.0)
Other	428/4953 (8.6)	392/4979 (7.9)
No procedure performed	42/4998 (0.8)	31/5012 (0.6)
Missing data	3/4998 (0.1)	2/5012 (<0.1)
Medications taken within 24 hr before surgery — no./total no. (%)		
Prophylactic-dose anticoagulant	626/4952 (12.6)	650/4978 (13.1)
Nonsteroidal antiinflammatory drug	470/4952 (9.5)	468/4978 (9.4)
COX-2 inhibitor	162/4951 (3.3)	165/4978 (3.3)
Statin	1815/4952 (36.7)	1842/4978 (37.0)
Beta-blocker	1153/4951 (23.3)	1206/4977 (24.2)
$P2Y_{12}$ inhibitor	3/4952 (0.1)	1/4978 (<0.1)
Perioperative antifibrinolytic agent — no./total no. (%)	73/4951 (1.5)	80/4977 (1.6)
Medications taken during first 3 days after surgery — no./total no. (%)		
Prophylactic-dose anticoagulant	3230/4948 (65.3)	3220/4976 (64.7)
Therapeutic-dose anticoagulant	225/4947 (4.5)	206/4976 (4.1)
Nonsteroidal antiinflammatory drug	1581/4947 (32.0)	1590/4976 (32.0)
COX-2 inhibitor	263/4947 (5.3)	270/4976 (5.4)
Statin	2071/4948 (41.9)	2100/4975 (42.2)
Beta-blocker	1428/4947 (28.9)	1498/4976 (30.1)
$P2Y_{12}$ inhibitor	59/4947 (1.2)	60/4976 (1.2)

* Plus–minus values are means ±SD. There were no significant differences between the two groups for any of the variables. IQR denotes interquartile range.
† Meeting this eligibility criterion involved meeting at least three of the nine risk criteria listed here.
‡ Major surgery was defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.
§ Patients may have undergone more than one type of surgery.

Appendix). In the initiation stratum, there were 3 strokes in the aspirin group and 12 in the placebo group (hazard ratio, 0.25; 95% CI, 0.07 to 0.89), whereas in the continuation stratum there were 13 strokes in the aspirin group and 7 in the placebo group (hazard ratio, 1.86; 95% CI, 0.74 to 4.66; P=0.19).

The effects of aspirin on myocardial infarction were similar in the initiation stratum and the continuation stratum (hazard ratio, 0.98; 95% CI, 0.79 to 1.22 in the initiation stratum; hazard ratio, 0.99; 95% CI, 0.79 to 1.24 in the continuation stratum; P=0.96 for interaction). In addition, the effects of aspirin on the composite of life-threatening or major bleeding were similar in the initiation stratum and the continuation stratum (hazard ratio, 1.24; 95% CI, 0.99 to 1.55 in the initiation stratum; hazard ratio, 1.20; 95% CI, 0.94 to 1.55 in the continuation stratum; P=0.87 for interaction).

BLEEDING RISK

To better understand the risk of bleeding on the basis of the timing of administration of aspirin, we undertook post hoc analyses. Among patients who were alive and did not have life-threatening or major bleeding, we determined the subsequent risk of a composite of life-threatening or major bleeding until day 30, starting on the day of surgery and then starting on each day thereafter (Table 3).

The absolute increase in the risk of a composite bleeding outcome associated with aspirin was 1.2% from the day of surgery up to 30 days and 0.9% from day 4 after surgery up to 30 days. If a patient survived without the composite bleeding outcome until day 8 after surgery, the increase in risk from day 8 to day 30 was 0.3% (3 in 1000 patients).

Table S5 in the Supplementary Appendix shows the results of the post hoc multivariable analysis investigating potential factors associated with perioperative myocardial infarction. The composite of life-threatening or major bleeding was an independent predictor of myocardial infarction (hazard ratio, 1.82; 95% CI, 1.40 to 2.36; P<0.001).

DISCUSSION

In this trial, the use of low-dose perioperative aspirin, as compared with placebo, did not reduce the rate of a composite of death or nonfatal myocardial infarction (the primary outcome) or the rates of the two secondary composite out-

Table 2. Effects of Aspirin on 30-Day Outcomes.*

Outcome	Aspirin (N=4998)	Placebo (N=5012)	Hazard Ratio (95% CI)†	P Value
	no. (%)			
Primary composite outcome: death or nonfatal myocardial infarction	351 (7.0)	355 (7.1)	0.99 (0.86–1.15)	0.92
Secondary outcomes				
Death, nonfatal myocardial infarction, or nonfatal stroke	362 (7.2)	370 (7.4)	0.98 (0.85–1.13)	0.80
Death, nonfatal myocardial infarction, cardiac revascularization, nonfatal pulmonary embolism, or nonfatal deep venous thrombosis	402 (8.0)	407 (8.1)	0.99 (0.86–1.14)	0.90
Tertiary outcomes — no. (%)				
Death from any cause	65 (1.3)	62 (1.2)	1.05 (0.74–1.49)	0.78
Death from cardiovascular cause	35 (0.7)	35 (0.7)	1.00 (0.63–1.60)	0.99
Myocardial infarction	309 (6.2)	315 (6.3)	0.98 (0.84–1.15)	0.85
Nonfatal cardiac arrest	9 (0.2)	12 (0.2)	0.75 (0.32–1.79)	0.52
Cardiac revascularization	13 (0.3)	17 (0.3)	0.77 (0.37–1.58)	0.47
Pulmonary embolism	33 (0.7)	31 (0.6)	1.07 (0.65–1.74)	0.79
Deep-vein thrombosis	25 (0.5)	35 (0.7)	0.72 (0.43–1.20)	0.20
New clinically important atrial fibrillation	109 (2.2)	94 (1.9)	1.16 (0.88–1.53)	0.28
Peripheral arterial thrombosis	13 (0.3)	15 (0.3)	0.87 (0.41–1.83)	0.71
Amputation	10 (0.2)	13 (0.3)	0.77 (0.34–1.76)	0.54
Rehospitalization for cardiovascular reasons	70 (1.4)	54 (1.1)	1.30 (0.91–1.86)	0.15
Acute kidney injury with receipt of dialysis‡	33 (0.7)	19 (0.4)	1.75 (1.00–3.09)	0.05
Safety outcomes				
Life-threatening bleeding	87 (1.7)	73 (1.5)	1.19 (0.88–1.63)	0.26
Major bleeding	230 (4.6)	188 (3.8)	1.23 (1.01–1.49)	0.04
Clinically important hypotension	2143 (42.9)	2096 (41.8)	1.03 (0.97–1.09)	0.37
Stroke	16 (0.3)	19 (0.4)	0.84 (0.43–1.64)	0.62
Congestive heart failure	44 (0.9)	38 (0.8)	1.16 (0.75–1.79)	0.50
Infection	488 (9.8)	495 (9.9)	0.99 (0.87–1.12)	0.86
Sepsis	243 (4.9)	258 (5.2)	0.94 (0.79–1.13)	0.52

* Percentages were calculated with the use of the Kaplan–Meier method.
† Hazard ratios are for the aspirin group, as compared with the placebo group.
‡ For this outcome, an odds ratio is provided instead of a hazard ratio, because the date that patients first started dialysis was not known.

comes. The use of perioperative aspirin increased the risk of major bleeding (hazard ratio, 1.23; 95% CI, 1.01 to 1.49). The results with respect to the primary and secondary outcomes were consistent in the initiation stratum and the continuation stratum.

In a meta-analysis of data from trials involving more than 110,000 patients who were not undergoing surgery, the use of aspirin, for primary and for secondary prevention, reduced the relative risk of myocardial infarction by 20% and 25%, respectively.[9] In contrast, the Pulmonary Embolism Prevention (PEP) trial included 13,356 patients undergoing surgery for a hip fracture.[13] Patients received 160 mg of aspirin or placebo before surgery and daily for 35 days. Aspirin was associated with an increased risk of myocardial infarction (hazard ratio, 1.33; 95% CI, 1.00 to 1.78), although the number of myocardial infarctions (184) was much lower than that in our study (624; hazard ratio with aspirin, 0.98; 95% CI, 0.84 to 1.15).

Consistent with our findings, the PEP trial and other perioperative trials have shown that aspirin significantly increases the risk of bleeding requiring a transfusion.[13,14] In previous surgical trials with hundreds of venous thromboembolism events, the use of aspirin decreased the risk of deep-vein thrombosis and pulmonary embolism by one third.[13,14] In our study, relatively few patients had deep-vein thrombosis (60 patients) or pulmonary embolism (64 patients), and more patients in our study than in the PEP trial received concomitant anticoagulant prophylaxis (65.0% vs. 44.4%).

Observational data suggest that the discontinuation of aspirin before surgery results in an increased thrombotic risk.[19,23] In our study, among the 4382 patients in the continuation stratum, we found no increase in thrombotic events owing to preoperative withholding of aspirin.

In the nonoperative setting, aspirin prevents myocardial infarction in patients with or at risk for atherosclerotic disease. However, in our study, aspirin did not prevent perioperative myocardial infarction. We offer three potential explanations for this finding. First, previous studies and our post hoc multivariable analysis showed that major bleeding was associated with perioperative myocardial infarction.[3,24] The absolute increase in bleeding risk with aspirin is greater in the perioperative setting than the nonoperative setting. It is possible that aspirin prevented some perioperative myocardial infarctions through thrombus inhibition and caused some myocardial infarctions through bleeding and subsequent mismatch between the supply of and demand for myocardial oxygen, thus resulting in the overall neutral effect in our study. Second, the lower boundary of the hazard ratio for myocardial infarction was 0.84, and we cannot exclude the possibility of a missed moderate effect that would be consistent with results of other aspirin trials.[9] Third, coronary-artery thrombus may not be the dominant mechanism of perioperative myocardial infarction.[5,6]

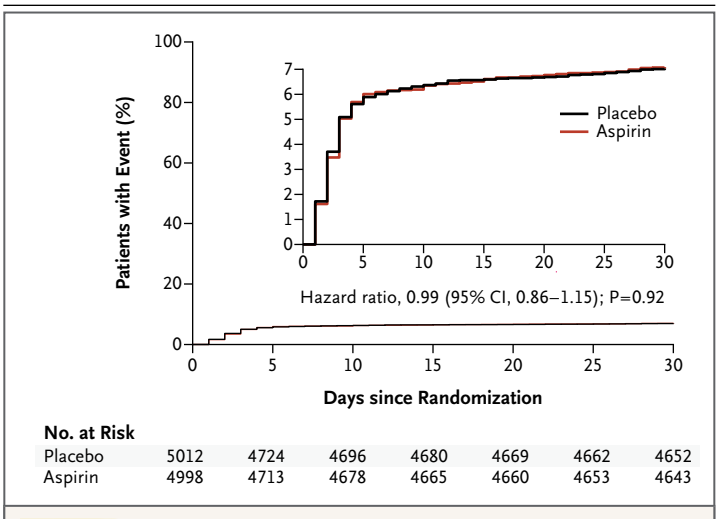

Figure 1. Kaplan–Meier Estimates of the Primary Composite Outcome of Death or Nonfatal Myocardial Infarction at 30 Days.

The inset shows the same data on an enlarged y axis.

The results with respect to the primary and secondary outcomes were similar across the two aspirin strata. There were significant between-group differences in one tertiary outcome (acute kidney injury with receipt of dialysis) and two safety outcomes (major bleeding and stroke) in one aspirin stratum but not the other (Table S4 in the Supplementary Appendix). The interaction P value for the aspirin stratum was not significant for two of these outcomes (i.e., acute kidney injury with receipt of dialysis and major bleeding), suggesting that there is no significant difference in effect across the aspirin strata for these two outcomes and that the results in the overall population provide the most reliable effect estimates.

Our data suggest that among patients on a long-term aspirin regimen, stopping aspirin 3 or

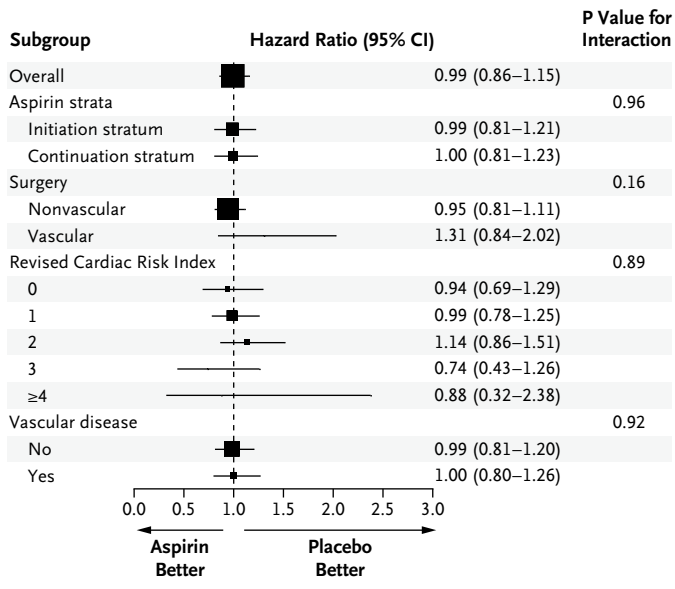

Figure 2. Subgroup Analyses of the Primary Outcome.

The primary composite outcome was death or nonfatal myocardial infarction at 30 days. The area of each square is proportional to the size of the corresponding subgroup. The Revised Cardiac Risk Index ranges from 0 to 6, with higher scores indicating greater risk.

more days before surgery may decrease the risk of major bleeding. Because we did not randomly assign patients according to the timing of aspirin cessation before surgery, we cannot determine the most effective timing to minimize bleeding risk. Studies have suggested that hemostasis is unimpaired if at least 20% of the platelets have normal COX-1 activity[25,26] and 12% of circulating platelets are replaced every 24 hours.[27,28] Therefore, stopping aspirin 72 or more hours before surgery may be adequate to minimize the risk of perioperative bleeding.

We observed one significant interaction: aspirin appeared to reduce the incidence of stroke in the initiation stratum but not in the continuation stratum (P=0.01 for interaction). Several considerations suggest that this is a spurious subgroup effect.[29] First, there were only 15 strokes in the initiation stratum, so the power to detect a change is small. Second, the effect of aspirin on reducing the risk of stroke in the initiation stratum was large (hazard ratio, 0.25), an effect that was inconsistent with the effect in the nonoperative setting on the basis of analyses of more than 1000 strokes and the perioperative data

Table 3. Absolute Increase in the Risk of a Composite of Life-Threatening or Major Bleeding with Aspirin Therapy, Starting on Each of the First 10 Postoperative Days until 30 Days after Surgery.*

Day at Start of Risk Analysis	Aspirin†	Placebo†	Absolute Increase in Risk with Aspirin	P Value
	no./total no. (%)		*percentage points*	
Day of surgery	311/4953 (6.3)	254/4978 (5.1)	1.2	0.01
Day 1 after surgery	191/4832 (4.0)	129/4852 (2.7)	1.3	<0.001
Day 2 after surgery	138/4779 (2.9)	92/4813 (1.9)	1.0	0.002
Day 3 after surgery	102/4741 (2.2)	59/4777 (1.2)	1.0	<0.001
Day 4 after surgery	73/4710 (1.6)	33/4748 (0.7)	0.9	<0.001
Day 5 after surgery	59/4693 (1.3)	27/4739 (0.6)	0.7	<0.001
Day 6 after surgery	43/4674 (0.9)	25/4736 (0.5)	0.4	0.03
Day 7 after surgery	39/4667 (0.8)	22/4731 (0.5)	0.3	0.03
Day 8 after surgery	20/2623 (0.8)	14/2662 (0.5)	0.3	0.29
Day 9 after surgery	15/2617 (0.6)	14/2660 (0.5)	0.1	0.82
Day 10 after surgery	14/2614 (0.5)	12/2657 (0.5)	0.0	0.67

* Among patients who were alive and had not already had life-threatening or major bleeding, we determined the risk of the composite of life-threatening or major bleeding until day 30, starting on the day of surgery and then on each subsequent day. We also determined the absolute increase in risk among patients in the aspirin group and the P value for the comparison between aspirin and placebo. This allows the inference that, for example, if aspirin is started on the day of surgery, the cumulative incremental risk of bleeding attributable to aspirin over the next 30 days is 1.2%. If aspirin had been started on day 4 after surgery, the cumulative incremental risk over the next 26 days would be 0.9%, and so forth. Starting on day 8 after surgery, the sample was restricted to patients in the initiation stratum because all patients in the continuation stratum stopped taking the study drug in the aspirin trial on day 8 after surgery and resumed their regular aspirin regimen.

† Percentages were calculated with the use of the Kaplan–Meier method.

from the PEP trial with 103 strokes (hazard ratio for aspirin, 1.10; 95% CI, 0.75 to 1.62).[9,13] Third, since this analysis was 1 of 19 tertiary or safety subgroup analyses that we performed, the results may be a chance finding. Finally, our hypothesized direction was opposite to that observed (i.e., we expected more benefit in the continuation stratum because of an aspirin-withdrawal effect). Therefore, the best estimate of the effect of aspirin on stroke is probably reflected in the overall population (hazard ratio, 0.84; 95% CI, 0.43 to 1.64).

If clinicians plan to use an anticoagulant agent for perioperative prevention of venous thromboembolism, our results suggest that starting or continuing aspirin throughout the perioperative period will provide no additional benefit but will increase the risk of major bleeding. However, our findings do not resolve the issue of the relative merits of aspirin versus other anticoagulant agents for perioperative thromboprophylaxis.[30] Although the POISE-2 trial is a large study by perioperative standards, the lower boundary (0.86) and upper boundary (1.15) of the hazard ratio for the primary outcome show that we have not excluded the possibility of appreciable benefit or harm.

It should be noted that we excluded patients who received a bare-metal coronary stent less than 6 weeks before surgery or a drug-eluting coronary stent less than 1 year before surgery. Observational data have suggested that perioperative aspirin prevents myocardial infarction and stent thrombosis in these two groups of patients.[31]

For patients on a long-term aspirin regimen, the most effective time to restart aspirin would be 8 to 10 days after surgery, when the bleeding risk has diminished considerably. If physicians consider starting aspirin after surgery to treat a thrombotic event (e.g., stroke or myocardial infarction), they can expect an absolute increase of 1.0 to 1.3 percentage points in the risk of life-threatening or major bleeding if aspirin is administered within the first 2 days after surgery. Physicians and their patients will have to weigh this risk against the high risk of death from the thrombotic event and the potential benefits of aspirin.[3,12,16]

In conclusion, the administration of aspirin before noncardiac surgery and throughout the early postsurgical period had no significant effect on the rate of death or nonfatal myocardial infarction but increased the risk of major bleeding. These findings apply both to patients who were not already receiving aspirin and to those who were on a long-term aspirin regimen.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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SUPPLEMENTAL APPENDICES

Section 1. Eligibility criteria

Inclusion criteria – patients ≥45 years of age undergoing in-hospital noncardiac surgery had to fulfill 1 or more of the following 5 inclusion criteria:

1. history of coronary artery disease,
2. history of peripheral arterial disease,
3. history of stroke,
4. undergoing major vascular surgery, OR
5. any 3 of 9 risk criteria
    - A. age ≥70 years;
    - B. undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery;
    - C. history of congestive heart failure
    - D. history of transient ischemic attack;
    - E. diabetes and currently taking an oral hypoglycemic agent or insulin;
    - F. history of hypertension;
    - G. preoperative serum creatinine >175 μmol/L (>2.0 mg/dl);
    - H. smoking within 2 years of surgery; or
    - I. undergoing emergent/urgent surgery

Exclusion criteria – patients fulfilling any of the following criteria were excluded:
1. hypersensitivity or known allergy to aspirin or clonidine;
2. consumption of aspirin within 72 hours prior to surgery;
3. systolic blood pressure <105 mm Hg;
4. heart rate <55 beats per minute or second or third degree heart block in a patient who did not have a permanent pacemaker;
5. active peptic ulcer disease or gastrointestinal bleeding within 6 weeks before surgery;
6. intracranial hemorrhage in the 6 months before surgery;
7. subarachnoid hemorrhage or epidural hematoma unless the event occurred more than 6 months before surgery and the abnormality was repaired;
8. drug-eluting coronary stent <1 year before surgery;
9. bare-metal coronary stent <6 weeks before surgery;
10. taking a thienopyridine or ticagrelor within 72 hours before surgery or intent to use one of these drugs during the first 7 days after surgery;
11. taking an alpha-2 agonist, alpha methyldopa, monoamine oxidase inhibitors, or reserpine before surgery;
12. planned use of therapeutic dose anticoagulation during the first 3 days after surgery;
13. undergoing intracranial surgery, carotid endarterectomy, or retinal surgery;
14. not consenting to participate in POISE-2 before surgery; OR
15. previously enrolled in POISE-2

Section 2. Follow-up process

Patients had a troponin measurement (or creatine kinase – myocardial band [CK-MB] if troponin was not available) drawn 6-12 hours after surgery and on the first, second, and third days postoperatively. Patients had electrocardiography when an elevated troponin or CK-MB measurement was detected. Research personnel at participating centers followed patients until 30 days after randomization, collected the data, and submitted the case report forms and supporting event documentation directly to the data management system.

Section 3. Secondary, tertiary, and safety outcomes up to 30 days after randomization

Secondary efficacy outcomes

Secondary outcomes included the following two composite outcomes: 1. mortality, nonfatal myocardial infarction, and nonfatal stroke; and 2. mortality, nonfatal myocardial infarction, cardiac revascularization procedure, nonfatal pulmonary embolism, and nonfatal deep venous thrombosis.

Tertiary efficacy outcomes

Tertiary efficacy outcomes included: 1. mortality; 2. vascular mortality; 3. myocardial infarction; 4. nonfatal cardiac arrest; 5. cardiac revascularization procedure; 6. pulmonary embolism; 7. deep venous thrombosis; 8. clinically important atrial fibrillation; 9. peripheral arterial thrombosis; 10. amputation; 11. re-hospitalization for vascular reasons; 12. acute kidney injury with receipt of dialysis; 13. length of hospital stay; and 14. length of intensive care unit / cardiac care unit stay

Safety outcomes

The safety outcomes included: 1. life-threatening bleed; 2. major bleed; 3. clinically important hypotension; 4. stroke; 5. congestive heart failure; 6. infection; and 7. sepsis.

Section 4. Outcome definitions

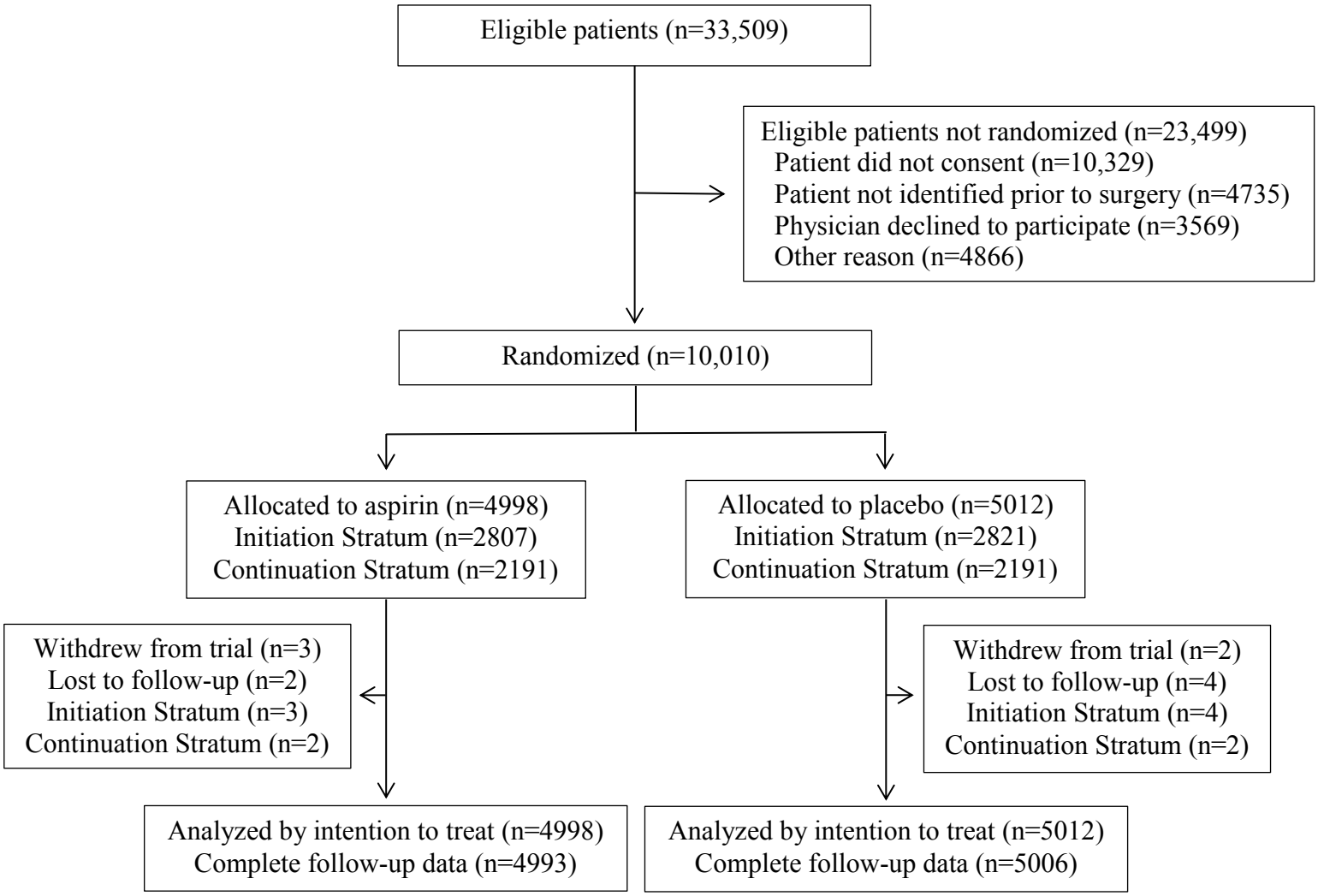
Outcome	Definition
Sub classification of death	Vascular death was defined as any death with a vascular cause and included those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolism, hemorrhage, or deaths due to an unknown cause. Non-vascular death was defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).
Myocardial infarction	The diagnosis of myocardial infarction required any one of the following criterion: 1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also required that 1 of the following was also present: A. ischemic signs or symptoms; B. development of pathologic Q waves; C. electrocardiography (ECG) changes indicative of ischemia; D. coronary artery intervention (i.e., PCI or CABG surgery); or E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; 2. Pathologic findings of an acute or healing myocardial infarction; or 3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.
Nonfatal cardiac arrest	Nonfatal cardiac arrest was defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Cardiac revascularization procedure	Cardiac revascularization procedure was defined as PCI or CABG surgery.

Stroke	Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.
Pulmonary embolism	The diagnosis of pulmonary embolism required any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical computed tomography (CT) scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan; or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan.
Deep venous thrombosis of leg or arm	The diagnosis of deep venous thrombosis required any one of the following: 1. A persistent intraluminal filling defect on contrast venography; 2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or 3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.
New clinically important atrial fibrillation	New clinically important atrial fibrillation was defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Peripheral arterial thrombosis	The diagnosis of peripheral arterial thrombosis required clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we required at least one of the following objective findings of peripheral arterial thrombosis: 1. Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism; 2. Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism; 3. Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism; or 4. Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism.

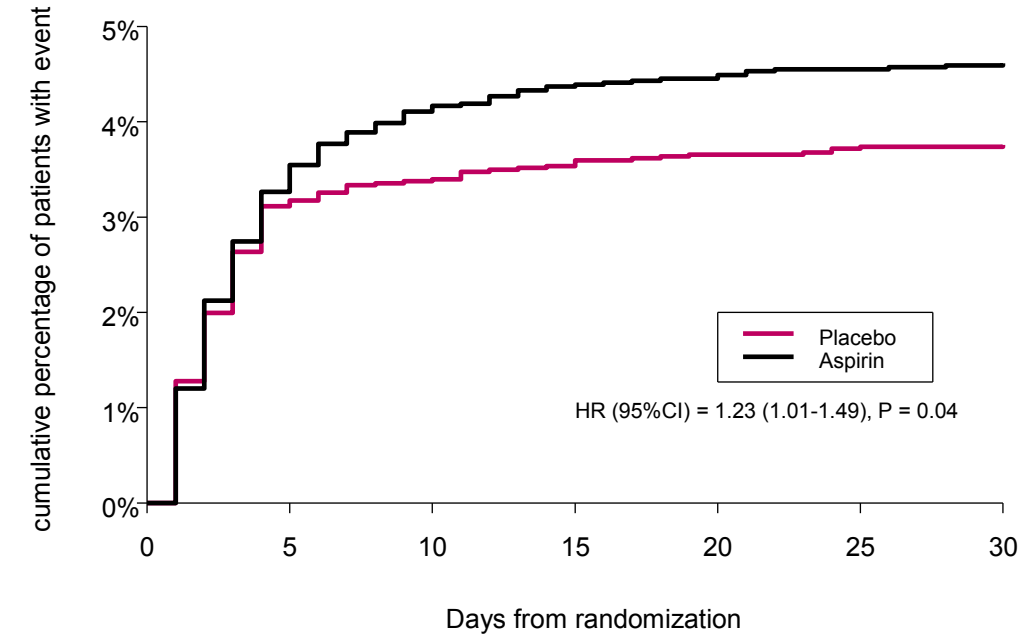
Amputation	Amputation was defined as an amputation procedure subsequent to the initial surgery.
Re-hospitalization for vascular reasons	Re-hospitalization for vascular reasons was defined as re-hospitalization for myocardial infarction, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolism, any vascular surgery, or bleeding.
Acute kidney injury with receipt of dialysis	Acute kidney injury with receipt of dialysis was defined as a patient who was not on dialysis prior to randomization but who developed acute kidney injury and received dialysis within 30 days of randomization. Dialysis was defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.
Life-threatening bleed	A life-threatening bleed was defined as a bleeding event that was fatal or led to: significant hypotension that required inotrope or vasopressor therapy, emergent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleed	A major bleed was defined as a bleeding event that was not specified under life- threatening bleeding and resulted in any one of the following: 1. a hemoglobin ≤70 g/L and the patient received a transfusion of ≥2 units of red blood cells; 2. a hemoglobin drop of ≥50 g/L and the patient received a transfusion of ≥2 units of red blood cells; 3. the patient received a transfusion of ≥4 units of red blood cells within a 24 hour period; 4. any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or 5. retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.
Clinically important hypotension	Clinically important hypotension was defined as a systolic blood pressure <90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.

Congestive heart failure	The definition of congestive heart failure required at least one of the following clinical signs (i.e., an elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
Infection	Infection was defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by a pathogenic organism.
Sepsis	Sepsis was defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response required 2 or more of the following factors: core temperature >38^{o}C or <36^{o}C; heart rate >90 beats per minute; respiratory rate >20 breaths/minute; white blood cell count >12 x 10^{9}/L or <4 x 10^{9}L.

Supplemental Figure 1: Trial flow diagram



Supplemental Figure 2: Kaplan-Meier estimates of major bleed



No. at Risk							
Placebo	5012	4842	4817	4798	4782	4773	4766
Aspirin	4998	4823	4764	4743	4734	4722	4710

Supplemental Table 1: Adherence to trial medication

Adherence	Aspirin (N=4998)	Placebo (N=5012)
Took 100% of study drug – no. (%)	3613 (72.7)	3706 (74.4)
Took ≥80% of study drug – no. (%)	3995 (80.4)	4108 (82.4)

Supplemental Table 2: Effects of Aspirin on the 30-day outcomes in the Initiation Stratum

Outcome	Aspirin (N=2807)	Placebo (N=2821)	Hazard Ratio (95% CI)	P Value
Primary outcome – no. (%)				
mortality or nonfatal myocardial infarction	182 (6.5)	185 (6.6)	0.99 (0.81-1.21)	0.92
Secondary outcomes – no. (%)				
mortality, nonfatal myocardial infarction, or nonfatal stroke	185 (6.6)	195 (6.9)	0.95 (0.78-1.17)	0.64
second composite outcome*	206 (7.3)	214 (7.6)	0.97 (0.80-1.17)	0.73
Tertiary outcomes – no. (%)				
total mortality	38 (1.4)	38 (1.3)	1.01 (0.64-1.58)	0.98
vascular mortality	19 (0.7)	19 (0.7)	1.01 (0.53-1.90)	0.99
myocardial infarction	158 (5.6)	162 (5.7)	0.98 (0.79-1.22)	0.86
nonfatal cardiac arrest	4 (0.1)	8 (0.3)	0.50 (0.15-1.67)	0.26
cardiac revascularization	3 (0.1)	7 (0.2)	0.43 (0.11-1.67)	0.22
pulmonary embolism	15 (0.5)	19 (0.7)	0.79 (0.40-1.56)	0.50
deep venous thrombosis	15 (0.5)	21 (0.7)	0.72 (0.37-1.39)	0.33
new clinically important atrial fibrillation	51 (1.8)	53 (1.9)	0.97 (0.66-1.42)	0.87
peripheral arterial thrombosis	5 (0.2)	8 (0.3)	0.63 (0.21-1.92)	0.41
amputation	5 (0.2)	8 (0.3)	0.63 (0.21-1.92)	0.41
re-hospitalization for vascular reasons	38 (1.4)	35 (1.3)	1.09 (0.69-1.73)	0.71
acute kidney injury with receipt of dialysis†	14 (0.5)	11 (0.4)	1.28 (0.58-2.83)	0.54
Safety outcomes – no. (%)				
life-threatening bleeding	49 (1.7)	47 (1.7)	1.05 (0.70-1.56)	0.82
major bleeding	130 (4.6)	98 (3.5)	1.34 (1.03-1.74)	0.03
clinically important hypotension	1207 (43.0)	1175 (41.7)	1.04 (0.96-1.12)	0.38
stroke	3 (0.1)	12 (0.4)	0.25 (0.07-0.89)	0.03
congestive heart failure	21 (0.8)	21 (0.7)	1.00 (0.55-1.84)	0.99
infection	291 (10.4)	289 (10.3)	1.01 (0.86-1.19)	0.89
sepsis	144 (5.1)	156 (5.6)	0.93 (0.74-1.16)	0.51

* the second composite outcome was a composite of mortality, nonfatal myocardial infarction, cardiac revascularization procedure, nonfatal pulmonary embolism, or nonfatal deep venous thrombosis.

† for this outcome we report the odds ratio instead of the hazard ratio, because we did not collect the actual date patients first started dialysis.

Supplemental Table 3: Effects of Aspirin on the 30-day outcomes in the Continuation Stratum

Outcome	Aspirin (N=2191)	Placebo (N=2191)	Hazard Ratio (95% CI)	P Value
Primary outcome – no. (%)				
mortality or nonfatal myocardial infarction	169 (7.7)	170 (7.8)	1.00 (0.81-1.23)	0.97
Secondary outcomes – no. (%)				
mortality, nonfatal myocardial infarction, or nonfatal stroke	177 (8.1)	175 (8.0)	1.01 (0.82-1.25)	0.90
second composite outcome*	196 (9.0)	193 (8.8)	1.02 (0.83-1.24)	0.86
Tertiary outcomes – no. (%)				
total mortality	27 (1.2)	24 (1.1)	1.12 (0.65-1.95)	0.67
vascular mortality	16 (0.7)	16 (0.7)	1.00 (0.50-2.00)	1.00
myocardial infarction	151 (6.9)	153 (7.0)	0.99 (0.79-1.24)	0.93
nonfatal cardiac arrest	5 (0.2)	4 (0.2)	1.25 (0.34-4.66)	0.74
cardiac revascularization	10 (0.5)	10 (0.5)	1.00 (0.42-2.40)	1.00
pulmonary embolism	18 (0.8)	12 (0.6)	1.50 (0.72-3.12)	0.27
deep venous thrombosis	10 (0.5)	14 (0.6)	0.71 (0.32-1.61)	0.41
new clinically important atrial fibrillation	58 (2.7)	41 (1.9)	1.42 (0.95-2.11)	0.09
peripheral arterial thrombosis	8 (0.4)	7 (0.3)	1.14 (0.41-3.15)	0.80
amputation	5 (0.2)	5 (0.2)	1.00 (0.29-3.45)	1.00
re-hospitalization for vascular reasons	32 (1.5)	19 (0.9)	1.69 (0.96-2.98)	0.07
acute kidney injury with receipt of dialysis†	19 (0.9)	8 (0.4)	2.41 (1.05-5.51)	0.04
Safety outcomes – no. (%)				
life-threatening bleeding	38 (1.7)	26 (1.2)	1.46 (0.89-2.41)	0.13
major bleeding	100 (4.6)	90 (4.1)	1.11 (0.84-1.48)	0.47
clinically important hypotension	936 (42.7)	921 (42.0)	1.02 (0.93-1.11)	0.72
stroke	13 (0.6)	7 (0.3)	1.86 (0.74-4.66)	0.19
congestive heart failure	23 (1.1)	17 (0.8)	1.35 (0.72-2.54)	0.34
infection	197 (9.0)	206 (9.4)	0.96 (0.79-1.16)	0.66
sepsis	99 (4.5)	102 (4.7)	0.97 (0.74-1.28)	0.83

* the second composite outcome was a composite of mortality, nonfatal myocardial infarction, cardiac revascularization procedure, nonfatal pulmonary embolism, or nonfatal deep venous thrombosis.

† for this outcome we report the odds ratio instead of the hazard ratio, because we did not collect the actual date patients first started dialysis.

Supplemental Table 4: Strata subgroup analyses for acute kidney injury with receipt of dialysis, stroke, and bleeding

Outcome	Aspirin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	P Value	Interaction P value
Acute kidney injury with receipt of dialysis*					
overall trial population	33/4886 (0.7)	19/4921 (0.4)	1.75 (1.00-3.09)	0.05	
aspirin initiation stratum	14/2748 (0.5)	11/2766 (0.4)	1.28 (0.58-2.83)	0.54	0.28
aspirin continuation stratum	19/2138 (0.9)	8/2155 (0.4)	2.41 (1.05-5.51)	0.04	
Stroke					
overall trial population	16/4998 (0.3)	19/5012 (0.4)	0.84 (0.43-1.64)	0.62	
aspirin initiation stratum	3/2807 (0.1)	12/2821 (0.4)	0.25 (0.07-0.89)	0.03	0.01
aspirin continuation stratum	13/2191 (0.6)	7/2191 (0.3)	1.86 (0.74-4.66)	0.19	
Major bleed					
overall trial population	230/4998 (4.6)	188/5012 (3.8)	1.23 (1.01-1.49)	0.04	
aspirin initiation stratum	130/2807 (4.6)	98/2821 (3.5)	1.34 (1.03-1.74)	0.03	0.35
aspirin continuation stratum	100/2191 (4.6)	90/2191 (4.1)	1.11 (0.84-1.48)	0.47	
Life-threatening or major bleed†					
overall trial population	312/4998 (6.3)	256/5012 (5.1)	1.22 (1.04-1.44)	0.02	
aspirin initiation stratum	176/2807 (6.3)	143/2821 (5.1)	1.24 (0.99-1.55)	0.06	0.87
aspirin continuation stratum	136/2191 (6.2)	113/2191 (5.2)	1.20 (0.94-1.55)	0.14	

* For this outcome we report the odds ratio instead of the hazard ratio, because we did not collect the actual date patients first started dialysis.

† To offer further insights into the impact of aspirin on bleeding events, we evaluated the post-hoc composite of life-threatening bleed and major bleed.

Supplemental Table 5: Independent predictors of myocardial infarction*

Independent predictors	Prevalence of predictors no. (%)	Patients having myocardial infarction in the 30 days after randomization		Adjusted hazard ratio (95% CI)	P value	PAR (95% CI)
		no.	% (95% CI)			
Preoperative independent predictors						
history of coronary artery disease	2268 (22.7)	186	29.8 (26.2-33.4)	1.49 (1.25-1.78)	<0.001	10.3 (6.4-16.3)
history of peripheral vascular disease	865 (8.6)	100	16.0 (13.1-18.9)	2.10 (1.69-2.60)	<0.001	8.9 (6.1-12.7)
history of congestive heart failure	337 (3.4)	39	6.3 (4.4-8.1)	1.60 (1.15-2.22)	0.005	2.5 (1.1-5.7)
eGFR <60 ml/minute/1.73m^2	2496 (25.4)	239	38.5 (34.7-42.4)	1.52 (1.28-1.79)	<0.001	13.9 (9.0-20.8)
age ≥75 years	3105 (31.0)	295	47.3 (43.4-51.2)	1.89 (1.60-2.23)	<0.001	23.5 (17.9-30.1)
Intraoperative and postoperative predictors						
clinically important hypotension	4217 (42.1)	319	51.1 (47.2-55.0)	1.37 (1.16-1.62)	<0.001	14.8 (8.8-23.7)
all major bleeds[†]	527 (5.3)	65	10.4 (8.0-12.8)	1.82 (1.40-2.36)	<0.001	5.0 (2.9-8.4)

PAR = population attributable risk; eGFR = estimated glomerular filtration rate

* We undertook a multivariable logistic regression analysis to determine the independent predictors of myocardial infarction. In this model the dependent variable was myocardial infarction at 30-days after randomization and we included potential independent preoperative variables that we had previously established were independent predictors of perioperative myocardial infarction in prior studies (i.e., history of stroke; hypertension; congestive heart failure; coronary artery disease; peripheral vascular disease; diabetes and taking medical treatment; preoperative estimated eGFR [<60 ml/minute/1.73m^2, and reference group ≥60 ml/minute/1.73m^2]; age ≥75 years; every 10-beats/minute increase in baseline heart rate; and urgent/emergent surgery) and potential independent intraoperative and postoperative variables that occurred before myocardial infarction (i.e., clinically important bradycardia, clinically important hypotension, all major bleeds put in the model as time-dependent variables).

[†] Composite of life threatening bleed and major bleed

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. DOI: 10.1056/NEJMoa1401105

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This supplement contains the following items:

Protocol:

1. Initial protocol (December 10, 2009) Pages 2 - 46
2. Final protocol (April 6, 2011) Pages 47 - 93
3. Summary of protocol changes Pages 94 - 101

Statistical Analysis Plan:

1. Initial statistical analysis plan (January 3, 2014) Pages 102 - 115
2. Final statistical analysis plan (January 24, 2014) Pages 116 - 129
3. Summary of statistical analysis plan changes Pages 130 - 132

POISE-2 Trial

PeriOperative ISchemic Evaluation-2 Trial

A large, international, placebo-controlled, factorial trial to assess the impact of clonidine and acetyl-salicylic acid (ASA) in patients undergoing noncardiac surgery who are at risk of a perioperative cardiovascular event

An International Collaborative Initiative

Study Coordinating Group and Central Address:

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Tel: 905-527-4322 ext. 40473
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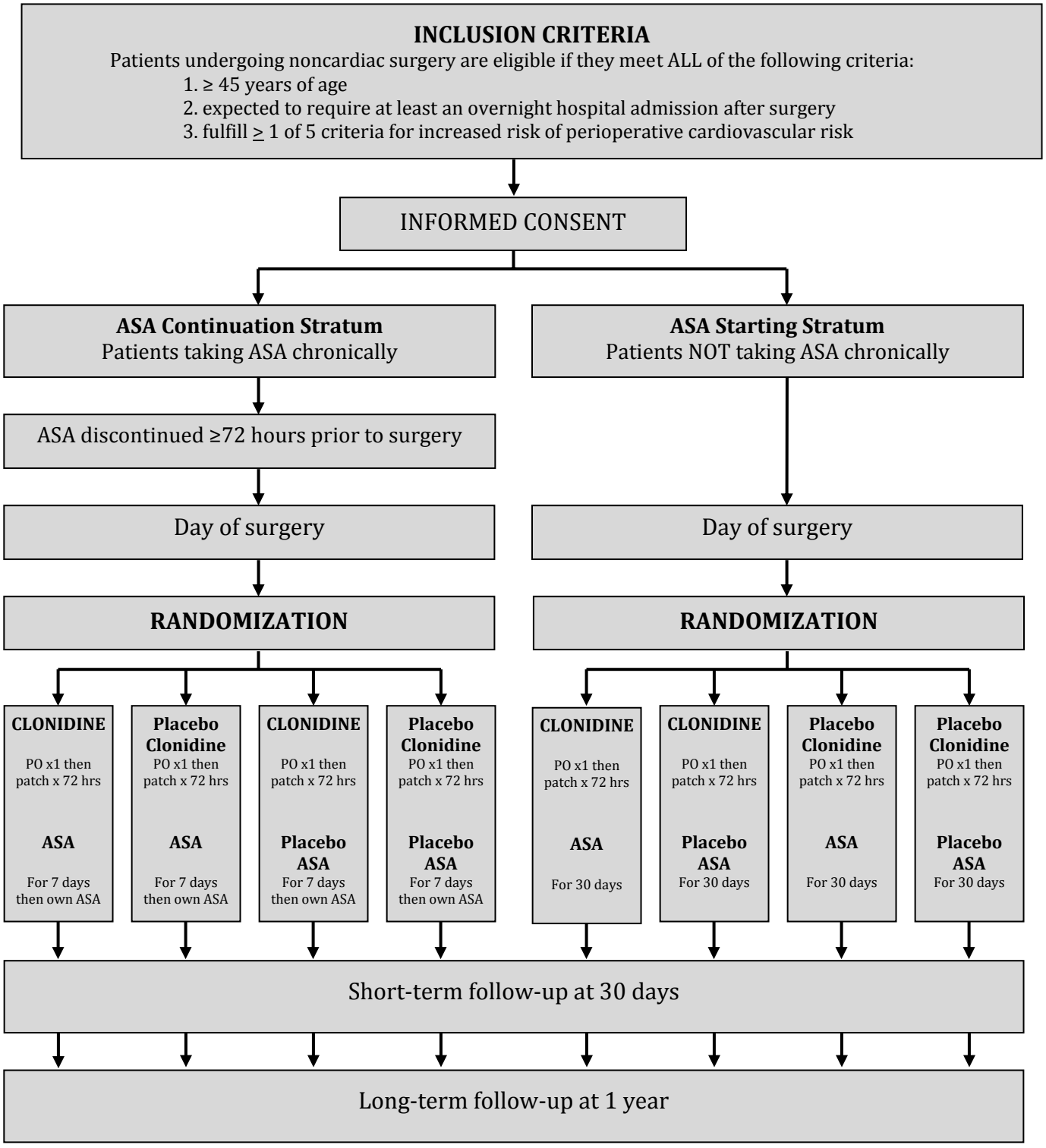
Date of original Protocol prior to commencing trial: December 10, 2009

Study Flow Chart



Title	**The PeriOperative Ischemic Evaluation-2 (POISE-2) Trial**
Project Office	POISE-2 Project Office Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Room C1-239 Hamilton, Ontario, Canada L8L 2X2
Study Size	10,000 patients
Study Design	Multicentre, international, blinded, 2x2 factorial randomized controlled trial of acetyl-salicylic acid (ASA) and clonidine.
Primary Objective	To determine the impact of clonidine versus placebo and ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.
Secondary Objective	To determine the impact of clonidine and ASA on cardiovascular events at 30 days and 1 year after surgery.
Inclusion Criteria	Patients undergoing noncardiac surgery are eligible if they: 1. are $\geq$ 45 years of age; 2. are expected to require at least an overnight hospital admission after surgery; AND 3. fulfill one or more of the following 5 criteria A. history of coronary artery disease; B. history of peripheral vascular disease; C. history of stroke; D. undergoing major vascular surgery; OR E. any 3 of the following 9 criteria: undergoing major surgery (i.e. intraperitoneal, intrathoracic, or major orthopedic surgery), history of congestive heart failure, transient ischemic attack, diabetes and currently taking an oral hypoglycemic agent or insulin, age $\geq$ 70 years, hypertension, serum creatinine > 175 µmol/L (> 2.0 mg/dl), history of smoking within 2 years of surgery, undergoing urgent/emergent surgery
Treatment Regimen	**Clonidine:** 2-4 hours prior to surgery, patients will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The patch will be removed at 72 hours after surgery. **ASA Continuation Stratum (patients taking ASA chronically):** Patients will be randomized to continue ASA or withdraw ASA and take a placebo starting on the day of surgery. Patients will continue taking the ASA trial intervention until 7 days after surgery after which patients will restart taking their regular ASA. **ASA Starting Stratum (patients not taking ASA chronically):** Patients will be randomized to start ASA or placebo on the day of surgery and will continue taking the ASA trial intervention until 30 days after surgery.

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1.0 INTRODUCTION AND RATIONALE

During the last few decades, substantial advances in noncardiac surgery have improved disease treatment and patients' quality of life. As a result, the number of patients undergoing noncardiac surgery is growing. A recent study that used surgical data from 56 countries suggests that 200 million major noncardiac surgical procedures are undertaken annually around the world.[1,2]

Noncardiac surgery is associated with major vascular complications (i.e., vascular death, nonfatal myocardial infarction [MI], nonfatal cardiac arrest, and nonfatal stroke). Worldwide, approximately 3-5 million adult patients annually suffer a major perioperative vascular complication in the first 30 days after surgery,[2] a number similar to the annual global incidence of new patients acquiring human immunodeficiency virus (HIV).[3] There is not a single established effective and safe intervention to prevent major perioperative vascular complications.[4] The striking absence of prophylactic interventions reflects the paucity of large randomized controlled trials (RCTs) evaluating perioperative interventions. Major perioperative vascular complications are therefore a major neglected public health problem.

We recently completed the largest RCT focused on cardiovascular complications in noncardiac surgery (the PeriOperative ISchemic Evaluation-1 [POISE-1] Trial).[5] In POISE-1, we randomized 8,351 patients with, or at risk of, atherosclerotic disease from 190 hospitals in 23 countries to receive extended-release metoprolol succinate (metoprolol CR) or placebo starting 2-4 hours prior to surgery and continuing for 30 days. Metoprolol decreased the 30-day risk of MI (hazard ratio [HR], 0.73; 95% CI, 0.60-0.89) but increased the risk of death (HR, 1.33; 95% CI, 1.03-1.74) and stroke (HR, 2.17; 95% CI, 1.26-3.74). These harmful consequences, unanticipated prior to POISE-1, have influenced thinking in this area and highlight the importance and need for large RCTs in perioperative medicine.

There are encouraging laboratory, physiology, operative and non-operative data suggesting that perioperative low-dose clonidine and low-dose acetyl-salicylic acid (ASA) may prevent all-cause mortality and nonfatal MI without excessive risk of major bleeding and clinically important hypotension. We will undertake a large international factorial RCT to establish the effects of these 2 interventions in patients undergoing noncardiac surgery. We call this RCT the POISE-2 Trial.

1.1 Principal Research Question

What is the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery?

1.2 Need for POISE-2 Trial

1.2.1 Pathophysiology of perioperative MI

MI is the most common major perioperative vascular complication. In the placebo group of the POISE-1 Trial 1.4% of the patients suffered a vascular death, 0.5% suffered a stroke, 0.5% suffered a nonfatal cardiac arrest, and 5.7% suffered an MI in the first 30 days.[5] Perioperative MI carries a poor prognosis. In the POISE-1 Trial 11.6% of the patients suffering a perioperative MI died within the first 30 days, and both asymptomatic and symptomatic perioperative MIs were powerful independent predictors of death at 30 days (odds ratio [OR] 3.45; 95% CI, 2.20-5.41 and OR 3.31; 95% CI, 1.78-6.15, respectively).[5] Further, a meta-analysis of noncardiac surgery studies suggests that an elevated troponin after surgery is a strong independent predictor of mortality up to 1 year after surgery (OR 6.7; 95% CI, 4.1-10.9).[6] Insights from the pathophysiology of perioperative MI may inform the type of intervention that will prevent this event.

Rupture of atherosclerotic plaque with superimposed arterial thrombosis constitutes the underlying pathophysiology in the majority of non-operative MIs.[7] Among patients suffering a non-operative MI, 64-100% have coronary artery plaque fissuring and 65-95% have an acute luminal thrombus.[8-13]

1.2.1.1 Potential role of supply-demand mismatch in the pathophysiology of perioperative MI

In contrast to non-operative MI, myocardial oxygen supply-demand mismatch represents a commonly proposed mechanism of perioperative MI.[14] Patients undergoing major noncardiac surgery experience an increase in sympathetic output and hence a rise in catecholamines[15-17] that result in an increase in heart rate and hence myocardial oxygen demand.[15 16] Noncardiac surgery is also associated with hypothermia that leads to shivering, which increases myocardial oxygen demand and is associated with myocardial ischemia.[18] In a coronary artery with a high grade stenosis, the supply response is limited, and can result in supply-demand mismatch MI when myocardial oxygen demand increases.

Consistent with this hypothesis, two small retrospective autopsy studies (<70 patients in total) reported that two-thirds of the patients who suffered a fatal perioperative MI had significant left main or 3 vessel coronary artery disease.[19 20] Most patients did not exhibit plaque fissuring and only about one-third had an intracoronary thrombus. Although the timing of the autopsies relative to the MIs may have allowed resolution of intracoronary thrombus, these data suggest that some fatal perioperative MIs are secondary to supply-demand mismatch.

1.2.1.2 Potential role of coronary thrombus in the pathophysiology of perioperative MI

An alternative mechanism of perioperative MI is that the acute stress of surgery and mechanical tissue injury induce a hypercoagulable-inflammatory state that increases the risk of coronary thrombus formation. The sympathetic hyperactivity associated with surgery promotes hypercoagulability by up-regulating coagulation and platelets and down-regulating fibrinolysis.[21-23] The increase in perioperative catecholamines is also associated with an increase in coronary shear stress, which may trigger plaque fissuring and acute coronary thrombosis.[24] Noncardiac surgery also results in inflammation (e.g., an increase in tumor necrosis factor α [TNF-α], interleukin [IL] -6, and IL-8) that may have a direct role in initiating plaque fissuring and acute coronary thrombosis.[25]

A small study of 21 patients who suffered a perioperative MI who had undergone a coronary angiography prior to vascular surgery revealed that the majority of nonfatal perioperative MIs occurred in arteries without a high-grade stenosis, suggesting that these events may have resulted from an acute coronary artery thrombosis.[26] Further evidence to support the thrombosis hypothesis comes from the Coronary Artery Revascularization Prophylaxis (CARP) Trial.[27] This trial randomized 510 patients undergoing elective vascular surgery who had at least one coronary artery with a $\geq$ 70% stenosis that was suitable for revascularization to receive coronary artery revascularization or no coronary artery revascularization before vascular surgery. This trial failed to demonstrate a significant reduction in the risk of perioperative MI in the patients randomized to undergo coronary revascularization. If supply-demand mismatch is the cause of perioperative MI, one would expect the risk of perioperative MI to decrease with coronary revascularization prior to noncardiac surgery.

Given the limitations of the evidence, it is not possible to draw firm conclusions regarding the pathophysiology of perioperative MI. It is likely that both mechanisms of perioperative MI (i.e., supply-demand mismatch and coronary thrombus) account for a portion of the perioperative MIs. Figure 1 summarizes the physiological changes that occur with surgery and how they may result in an MI. A perioperative prevention trial would ideally impact both proposed mechanisms to provide the greatest potential for benefit.

1.2.2 Laboratory and physiology evidence suggests clonidine may prevent death and nonfatal MIs in patients undergoing noncardiac surgery

Like beta-blockers, alpha-2 agonists (e.g., clonidine) attenuate the perioperative stress response, but they do so through a different mechanism. Alpha-2 agonists act on central and presynaptic receptors to inhibit the release of norepinephrine leading to a reduction in central sympathetic outflow.[28 29] Clonidine, the most available alpha-2 agonist, has a number of attributes that make it attractive as a potential agent to prevent perioperative MI and death. Perioperative clonidine induces sympatholysis,[30 31] has analgesic[32-34] and anti-shivering effects,[35] reduces myocardial oxygen uptake,[36] and reduces TNF-α, IL-6, and IL-8.[37 38] A meta-analysis of 2 noncardiac surgery clonidine RCTs (total 358 patients)

found a reduction in myocardial ischemia (based upon Holter recordings) with clonidine, without an increased risk of hemodynamic instability.[39] Perioperative clonidine trials have also demonstrated that clonidine decreases the average heart rate during the perioperative period.[30 31 40] Given these physiological changes, which may minimize the risk of supply-demand mismatch (i.e., sympatholytic, analgesic, and anti-shivering effects) and thrombus formation (i.e., sympatholytic, analgesic, and anti-inflammatory effects), clonidine may prevent major perioperative vascular events without incurring an increased risk of events mediated through hemodynamic instability, particularly stroke.

1.2.3 Experimental evidence and relevant systematic reviews evaluating the effects of alpha-2 agonists and clonidine in patients undergoing noncardiac surgery

1.2.3.1 Alpha-2 agonist data

A meta-analysis of alpha-2 agonists (clonidine, dexmedetomidine, mivazerol) included 12 noncardiac surgery RCTs.[41] The authors of this systematic review reported separately the results for patients who had vascular surgery and patients who had nonvascular noncardiac surgery. The meta-analysis demonstrated a statistically significant reduction in both death (39 events; relative risk [RR] 0.47; 95% CI, 0.25-0.90) and MI (110 events; RR 0.66; 95% CI 0.46-0.94) with alpha-2 agonist therapy among the vascular surgery patients. The investigators found no effect on mortality (31 events; RR 1.09; 95% CI 0.52-2.09) and MI (62 events; RR 1.25; 95% CI 0.83-2.21) among the nonvascular noncardiac surgery patients. The 6 trials that reported hypotension did not suggest an increase in hypotension with an alpha-2 agonist (RR 1.03; 95% CI 0.89-1.21).

The likelihood of a true subgroup effect is low.[42] Although there were 12 RCTs included in this meta-analysis, a single trial of mivazerol accounted for 80% of the deaths and 91% of the MIs.[43] While this trial randomized 2854 patients, the published report excludes 957 of these patients at high risk of coronary artery disease in whom an interim analysis demonstrated a lower than expected event rate.[43] The investigators reported on the remaining 1897 patients with established coronary artery disease among whom 91 (9.5%) assigned mivazerol and 100 (10.6%) assigned placebo suffered a death or nonfatal MI (risk ratio 0.89; 95% CI, 0.67-1.18). The authors reported a statistically significant reduction in this composite outcome with mivazerol only for the subgroup of vascular surgery patients, but there was no interaction P value reported and no prior hypothesis for a subgroup effect.

1.2.3.2 POISE-2 Pilot Trial

Since this prior meta-analysis, we have conducted the POISE-2 Pilot. We report here the data on the first 60 patients included in this pilot, Table 1. In the POISE-2 Pilot 6 of 30 clonidine patients versus 10 of 30 placebo patients developed clinically important hypotension. Although the POISE-2 Pilot is small these results are encouraging and suggest that the POISE-2 clonidine regimen may allow us to obtain the benefits we demonstrated in POISE-1 while mitigating the risks that appeared to have primarily occurred through clinically important hypotension.

1.2.3.3 Updated perioperative clonidine meta-analysis

The outdated perioperative clonidine meta-analysis mentioned above (section 1.2.2) included only 2 noncardiac surgery clonidine trials.[39] We therefore conducted a systematic review and meta-analysis of clonidine given to patients undergoing noncardiac surgery, which also includes the POISE-2 Pilot data. Thirty-two RCTs met our eligibility criteria.[30 31 33 36 37 40 44-68]

Table 2 reports the perioperative clonidine meta-analysis results. There was a statistically significant reduction in mortality with clonidine (RR 0.27; 95% CI, 0.07-0.99), but there were only 10 deaths in total making this result unreliable. The MI, stroke, and congestive heart failure results are also encouraging but limited by few events. Myocardial ischemia was less common among the patients randomized to clonidine (19.3%) compared to control (31.0%) (RR 0.66; 95% CI, 0.49-0.89).

Table 3 reports the clinically important hypotension results. The results demonstrate a significant increase in clinically important hypotension with clonidine (RR 1.51; 95% CI, 1.20-1.91), but there was moderate heterogeneity (I^2 31%). Our a priori hypothesis for heterogeneity based upon low-

dose clonidine (daily effective dose < 0.3 mg) versus high-dose clonidine (daily effective dose ≥ 0.3mg) explained this heterogeneity. The trials evaluating high-dose clonidine, but not those evaluating low-dose clonidine, demonstrated a significant increase in clinically important hypotension (P value for the test of interaction between these subgroups was < 0.01). Importantly, the low-dose clonidine trials showed the same positive trends as the high-dose clonidine trials regarding the other outcomes (e.g., mortality). Since clinically important hypotension had the largest population-attributable risk for stroke in POISE-1, the results suggest we will not find an increased risk of stroke with low-dose clonidine.

A meta-analysis of the low-dose clonidine RCTs demonstrates that low-dose clonidine reduces heart rate (mean difference = -5.94; 95% CI, -9.61, -2.27). No trials reported any rebound hypertension after discontinuation of the short courses of perioperative clonidine.

1.2.4 Perioperative clonidine may reduce intermediate-term mortality

An elevated troponin measurement after surgery is an independent predictor of death at 1 year. It has been hypothesized that perioperative ischemia results in unstable coronary plaques that are prone to fissuring weeks to months later, resulting in cardiac events.[69] This hypothesis, if correct, would explain how clonidine (which prevents perioperative myocardial ischemia) might, even after its discontinuation, affect intermediate-term (i.e., 1 year) vascular events.

Wallace and colleagues undertook an RCT evaluating the effect of 4 days of perioperative clonidine in patients undergoing noncardiac surgery.[31] Clonidine demonstrated an absolute risk reduction (ARR) of 5.4% for mortality at 30 days (total of 5 deaths, p=0.048) and demonstrated an ARR of 14% for mortality at 2 years (total of 38 deaths, p=0.035). These encouraging but limited data (Wallace is the only clonidine trial that reported following patients beyond 30 days) highlight the need for further RCTs to examine whether perioperative clonidine reduces intermediate-term mortality.

1.2.5 Current perioperative clonidine practices and feasibility of a perioperative clonidine RCT

We are currently conducting a 40,000 patient prospective cohort study (i.e., VISION) in 10 centres in 7 countries. VISION is evaluating a representative sample of patients ≥ 45 years of age who are undergoing noncardiac surgery. Of the first 6000 patients included in VISION, 2839 fulfilled the POISE-2 eligibility criteria and only 1.2% of these patients received an alpha-2 agonist sometime during the perioperative period. These data demonstrate that clonidine is used infrequently in the perioperative setting; indicating that the available information on clonidine has not impacted clinical practice. These data also indicate that it should not be difficult to recruit patients into a perioperative clonidine trial, as confirmed by our POISE-2 pilot where 3 centres enrolled 60 patients, and each centre recruited on average > 3 patients per week. The infrequent routine use of perioperative clonidine and our rapid recruitment rate in the POISE-2 Pilot demonstrate the feasibility of the POISE-2 Trial.

1.2.6 Observational and experimental evidence regarding the effects of initiating and withdrawing ASA in the <u>non-operative</u> setting

The Antithrombotic Trialists' Collaboration undertook a meta-analysis of RCTs evaluating the effects of initiating anti-platelet therapy. This non-operative meta-analysis included 195 trials involving 135,640 patients and 17,207 major vascular events. This meta-analysis demonstrated that ASA reduced nonfatal MI by one third, nonfatal stroke by one quarter, and mortality by one sixth in patients with or at high risk of atherosclerotic disease.[70] This meta-analysis also demonstrated that low-dose ASA (75-150 mg daily) was as effective but less gastrotoxic than higher doses, but in acute settings an initial loading dose of 160 mg of ASA (which is sufficient to provide rapid and complete inhibition of TXA_2 mediated platelet aggregation)[71] may be required.[72]

A recent meta-analysis of 3 prospective cohort studies that included 34,344 patients evaluated the effects of discontinuing ASA in the non-operative setting.[73] ASA discontinuation was associated with an increased risk for thrombotic events (RR 1.82; 95% CI, 1.52-2.18; $I^2 = 0\%$).

1.2.7 Laboratory and physiology evidence that suggests ASA may prevent vascular death and nonfatal myocardial infarctions in patients undergoing noncardiac surgery

Immediately after noncardiac surgery, patients experience a rise in circulating platelet release products.[74] Platelet surface catalyzing coagulation reactions facilitate thrombin generation and these events may promote thrombus formation and lead to arterial occlusion in the perioperative setting.[25] Acute withdrawal of chronic ASA results in a pro-thrombotic state (i.e., increased thromboxane A_2 [TXA_2] and decreased fibrinolysis).[75 76] Given these physiological changes, ASA initiation or, for chronic users, ASA continuation - and the associated inhibition of platelet aggregation - may prevent major perioperative vascular events through inhibition of thrombus formation.[77]

1.2.8 Experimental evidence and relevant systematic reviews evaluating the effects of ASA in patients undergoing noncardiac surgery

We have undertaken a systematic review and meta-analysis of perioperative ASA trials that included patients undergoing any type of noncardiac surgery. Fifteen RCTs fulfilled eligibility criteria and are included in our systematic review.[78-92]

Table 4 reports our perioperative ASA meta-analysis results. Both all-cause mortality (RR 0.85; 95% CI, 0.63-1.14) and vascular mortality (RR 0.59; 95% CI, 0.28-1.25) show trends towards benefit from perioperative ASA. In contrast, 58 of 9069 patients assigned ASA and 43 of 9037 patients assigned control suffered a nonfatal MI (RR 1.31; 95% CI, 0.88-1.94). This trend towards harm was identified in trials that did not routinely monitor daily cardiac biomarkers after surgery, except for the POISE-2 Pilot, and in total there were only a moderate number of nonfatal MIs. The meta-analysis did not demonstrate an impact on nonfatal stroke with perioperative ASA (total 125 events; RR 0.91; 95% CI 0.64-1.29), and suggested a trend towards fewer nonfatal pulmonary emboli with ASA (total 91 events; RR 0.74; 95% CI, 0.49-1.11). Perioperative ASA demonstrated an increase in major bleeding (total 357 events; RR 1.47; 95% CI, 1.19-1.80).

Although there were 19 trials in our ASA meta-analyses the Pulmonary Embolism Prevention (PEP) Trial dominated contributing the majority of patients and events.[85] PEP was a trial of hip fractures focused on pulmonary emboli, and they did not monitor for perioperative MI with daily troponin measurements. PEP provides important information, but there is a need for a large perioperative ASA trial that includes the majority of noncardiac surgeries and actively monitors for perioperative MIs.

1.2.9 Low versus high-dose ASA

The only surgical trial that has compared low versus high-dose ASA randomized patients undergoing carotid endarterectomy to low-dose ASA (i.e., 709 patients assigned 81 mg/day and 708 patients assigned 325 mg/day) and they had a lower risk (i.e., 6.2%) of the primary outcome (i.e., a composite of death, nonfatal MI, and nonfatal stroke at 3 months) than the patients randomized to high-dose ASA (i.e., 715 patients assigned 650 mg/day and 717 patients assigned 1300 mg/day) of which 8.4% suffered the primary outcome, P 0.03.[93] Recently the CURRENT OASIS-7 Trial was presented at the European Society of Cardiology 2009 Congress. This trial of 2 low-doses of ASA randomized 25,087 patients suffering an acute coronary syndrome to ASA 75-100 mg per day versus ASA 300-325 mg per day. At 30 day follow-up there was no difference between the groups regarding major cardiovascular outcomes (i.e., cardiovascular death, myocardial infarction, and stroke). Given this evidence we will evaluate low-dose ASA 81mg per day in POISE-2.

1.2.10 Current perioperative ASA practices and feasibility of a perioperative ASA trial

In POISE-1, 36.1% of the participants took ASA sometime in the week prior to surgery, and 39.7% took ASA sometime during their hospital admission. Because 84% of the patients in POISE-1 underwent general, orthopedic, or vascular surgery, we conducted a cross-sectional survey of all practicing Canadian general, orthopedic, and vascular surgeons.[94] Our survey demonstrated marked variations among surgeons regarding the starting and holding of ASA around the time of surgery. A majority of respondents also reported a willingness to have their patients participate in a perioperative ASA trial. Our survey identified the need for, and support of, a large randomized trial of perioperative ASA

among patients undergoing noncardiac surgery. Our recruitment rate in the POISE-2 Pilot demonstrates the feasibility of recruiting patients into a perioperative ASA trial.

1.2.11 Summary of why POISE-2 is needed now

Laboratory and physiology evidence suggests clonidine may minimize the risk of supply-demand mismatch and thrombus formation; perioperative trial evidence demonstrates clonidine prevents myocardial ischemia and suggests clonidine may prevent MI and mortality in both the short and intermediate-term. Perioperative trials also suggest low-dose clonidine does not result in hemodynamic instability, making an increase in stroke less likely. Despite this evidence, clonidine is uncommonly used in the perioperative setting. The need for a large adequately powered perioperative low-dose clonidine trial to settle the issue in a clear way that will drive subsequent practice is compelling.

Laboratory and physiological evidence suggests that ASA initiation or, for chronic users, ASA continuation may prevent major perioperative vascular events. The perioperative trial evidence suggests ASA may prevent mortality, but the effect on MI is unclear and the increased risk of bleeding is imprecise. There is overwhelming RCT evidence in the non-operative setting that ASA prevents death, MI, and, stroke. Observational data suggest that ASA discontinuation in the non-operative setting results in adverse thrombotic events. A perioperative carotid endarterectomy RCT of 2849 patients demonstrated improved outcomes with low-dose ASA compared to high-dose ASA. Our national survey demonstrates that perioperative ASA usage is variable, identifying the need for, and community interest in, a large perioperative low-dose ASA trial.

2.0 PLAN OF INVESTIGATION

2.1 Trial Objectives

2.1.1 Primary efficacy objectives

To determine the impact of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.

2.1.2 Secondary efficacy objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 30 days after randomization: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

2. To determine in each ASA stratum the impact on a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization.

2.1.3 Safety objectives

1. To determine the impact of perioperative low-dose clonidine on each of the following individual outcomes at 30 days after randomization: stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure.

2. To determine the impact of perioperative low-dose ASA on each of the following individual outcomes at 30 days after randomization: stroke, life-threatening bleeding, and major bleeding.

2.1.4 One year follow-up objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on all-cause mortality and nonfatal MI at 1 year after randomization.

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 1 year after randomization: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, and rehospitalization for vascular reason.

2.2 Trial Design

POISE-2 is an international RCT of 10,000 patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery. Utilizing a 2X2 factorial design, POISE-2 will determine the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo in the perioperative setting. Patients, health care providers, data collectors, and outcome adjudicators will be blind to treatment allocation.

2.3 Sample Size

Our perioperative meta-analysis suggested that clonidine had an RR of 0.27 for mortality and 0.45 for MI, but the confidence intervals were wide. Given the multitude of pathogenic mechanisms associated with perioperative MI, it is only realistic to expect a moderate relative treatment effect[95] (as was the case in POISE-1).[5] Therefore, we assume clonidine will result in a HR of 0.75 for the primary outcome (all-cause mortality or nonfatal MI). Our perioperative meta-analysis suggested ASA had a RR of 0.85 for all-cause mortality and 1.31 for nonfatal MI, but the confidence intervals were wide. The MI data are inconsistent with the overwhelming evidence in the non-operative setting in which ASA results in a RR of 0.70 for MI.[70] Further, the observational ASA withdrawal data suggest an increased risk of thrombotic events with ASA discontinuation.[73] Therefore, we believe it is more probable that ASA will result in a moderate treatment effect consistent with a HR of 0.75 for the primary outcome.

Table 5 presents our sample size calculations. We used the control event rate for all-cause mortality and nonfatal MI in POISE-1 and adjusted this event rate accounting for the factorial design (i.e., both interventions will have a HR of 0.75), and this suggests a placebo event rate of 6.1%. Our sample size calculation also takes into account patients discontinuing their study drug. We will undertake a trial of at least 10,000 patients as this will provide 84% power if our event rate is 6.1% and 81% power if our event rate is 5.6% (2-sided alpha = 0.05).

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients are eligible if they:

1. are undergoing noncardiac surgery;
2. are $\geq$ 45 years of age;
3. are expected to require at least an overnight hospital admission after surgery; AND
4. fulfill $\geq$ 1 of the following 5 criteria:
   - A. history of coronary artery disease as defined by any one of the following 6 criteria
     - i. history of angina
     - ii. history of a myocardial infarction or acute coronary syndrome
     - iii. history of a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging
     - iv. history of a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia
     - v. history of a coronary angiographic or CT coronary angiographic evidence of atherosclerotic stenosis $\geq$ 50% of the diameter of any coronary artery
     - vi. ECG with pathological Q waves in two contiguous leads
   - B. history of peripheral vascular disease as defined by a physician diagnosis of a current or prior history of any one of the following 4 criteria
     - i. intermittent claudication
     - ii. vascular surgery for atherosclerotic disease
     - iii. an ankle/arm systolic blood pressure ratio $\leq$ 0.90 in either leg at rest
     - iv. angiographic or doppler study demonstrating $\geq$ 70% stenosis in a noncardiac artery
   - C. history of stroke as defined by any one of the following 2 criteria
     - i. a physician diagnosis of stroke

ii. CT or MRI evidence of a prior stroke

D. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, and carotid endarterectomies; OR

E. any 3 of 9 risk criteria

i. undergoing major surgery defined as intraperitoneal, intrathoracic, or major orthopedic surgery (i.e., hip arthroplasty, internal fixation of hip or femur, pelvic arthroplasty, knee arthroplasty, above-knee amputation or amputation below the knee but above the foot)

ii. history of congestive heart failure defined as a physician diagnosis of a current or prior episode of congestive heart failure OR prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema

iii. history of a transient ischemic attack;

iv. diabetes and currently taking an oral hypoglycemic agent or insulin;

v. age $\geq$ 70 years;

vi. hypertension;

vii. serum creatinine > 175 μmol/L (> 2.0 mg/dl);

viii. history of smoking within 2 years of surgery;

ix. undergoing emergent/urgent surgery defined as surgery that a surgeon schedules to go to the operating room within 48 hours of an acute presentation to the hospital

3.2 Exclusion Criteria

We will exclude patients meeting any of the following criteria:

1. consumption of ASA within 72 hours prior to surgery;
2. hypersensitivity or known allergy to ASA or clonidine;
3. systolic blood pressure < 105 mm Hg;
4. heart rate < 55 beats per minute in a patient who does not have a permanent pacemaker;
5. second or third degree heart block without a permanent pacemaker;
6. active peptic ulcer disease;
7. drug-eluting coronary stent in the year prior to randomization;[96]
8. bare-metal coronary stent in the 6 weeks prior to randomization;[96]
9. currently taking an alpha-2 agonist, alpha methyldopa, reserpine, clopidogrel, or ticlopidine;
10. undergoing intracranial surgery, carotid endarterectomy, or retinal surgery;
11. not consenting to participate in POISE-2 prior to surgery; OR
12. previously enrolled in POISE-2 Trial

4.0 PATIENT RECRUITMENT AND INFORMED CONSENT

We will utilize efficient recruitment strategies we developed in POISE-1. In the majority of centres, research personnel will screen the patient list in the preoperative assessment clinic to identify eligible patients. Research personnel will use a variety of screening approaches to capture patients who do not attend the preoperative assessment clinic, including screening: the daily surgical list in the operating room, patients on surgical wards and intensive care units, and patients in the preoperative holding area. Centres will also use all potential patient sources including asking the services of anesthesia, surgery, and medicine to page the study personnel regarding all surgical admissions through the emergency department and consultations for ward patients requiring surgery. Research personnel will approach all eligible patients to obtain informed consent. POISE-2 will enroll patients from approximately 150 centres in 16 countries.

5.0 RANDOMIZATION

Randomization will occur 2-4 hours prior to surgery for all eligible patients for whom informed consent is obtained. Research personnel will randomize patients via a 24-hour computerized randomization phone service at the coordinating centre at the Population Health Research Institution (PHRI) at the Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. The

randomization process will use block randomization stratified by centre. Study centre personnel will not know the block size. We will randomize patients in a 1:1:1:1 fashion to receive clonidine/ASA, clonidine/ASA placebo, clonidine placebo/ASA, or clonidine placebo/ ASA placebo. Patients in the ASA Continuation Stratum and ASA Starting Stratum will be evenly assigned to each of the 4 randomization groups. Approximately half the POISE-2 patients will come from each ASA stratum (i.e., we will ensure that each ASA stratum constitutes as least 45% of the overall trial population, as we were able to achieve in the POISE-2 Pilot).

6.0 ADMINISTRATION OF STUDY MEDICATION

Medical orders will include all drug administration protocols.

6.1 Clonidine or Placebo

Prior to surgery (goal 2-4 hours) patients fulfilling hemodynamic requirements (i.e., systolic blood pressure $\geq$ 105 mm Hg and a heart rate $\geq$ 55 bpm) will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The clonidine patch releases clonidine at a constant rate (0.2 mg/day) for 7 days. Patients will have the patch removed at 72 hours after surgery. No cases of clonidine withdrawal hypertension have been reported with transdermal clonidine, therefore we do not require a tapering process.[97]

Oral clonidine is absorbed rapidly and reaches peak serum concentrations within 2-4 hours and demonstrates physiological effects (e.g., a decrease in heart rate) within 1 hour; these effects persist for 24 hours.[98 99] Transdermal clonidine reaches peak serum concentrations at 48 hours after application, demonstrates physiological effects at 24 hours; after removal of the clonidine patch serum concentrations and physiological effects can persist for 2 -3 days.[100] Giving oral clonidine 2-4 hours before surgery will allow us to achieve physiological effects before surgery and these effects will persist for 24 hours. Applying the transdermal patch 2-4 hours before surgery will allow us to achieve physiological effects starting around the time the effects of the oral clonidine dose are resolving. This dosing regimen is consistent with a low-dose clonidine regimen (i.e., an effective dose < 0.3 mg/day).

6.2 ASA or Placebo

We will enrol patients in 1 of 2 ASA strata. The ASA Continuation Stratum will involve patients who are taking ASA chronically; we will randomize these patients to continue ASA or withdraw ASA and take a placebo. The ASA Starting Stratum will involve patients who are not taking ASA chronically; we will randomize these patients to start ASA or placebo. All patients will be randomized on the day of surgery, and approximately half the POISE-2 patients will come from each ASA stratum, as supported by our prior research (i.e., POISE-2 Pilot). Patients in both ASA strata will receive the same trial ASA intervention (i.e., either ASA 81 mg or matching placebo). For the first dose prior to surgery (goal 2-4 hours) they will take 2 tablets orally. After the first dose, patients will take 1 tablet daily for 30 days in the Starting Stratum and 7 days in the Continuation Stratum, after which they will resume their regular ASA. Patients who are not able to take ASA orally will receive it rectally.

We will consider patients who have taken ASA daily for at least 1 month within a 6 week period prior to surgery to be on ASA chronically, and we will enrol these patients in the ASA Continuation Stratum. In this stratum, we will include patients who have had their ASA withheld sometime in the 2 weeks before surgery. No ASA is allowed for 72 hours prior to surgery (outside of the study drug), and if a patient has taken ASA in the 72 hours before surgery they are ineligible.

Our decision to allow patients to participate in the Continuation Stratum even if they have taken their ASA 73 hours prior to surgery was based upon the following 2 points. First, the mean life span of human platelets is approximately 8 to 10 days, and about 12% of circulating platelets are replaced every 24 hours.[101 102] In patients treated with ASA it may take 10 days for the total platelet population to be renewed, and thus restore normal COX-1 activity. O'Brien has demonstrated, however, that abnormal platelet aggregation after ingestion of aspirin can be corrected ex vivo by 10% normal platelet rich plasma.[102] Further, it has been reported that if as little as 20% of platelets have normal COX-1 activity,

hemostasis is normal.[103 104] Therefore stopping ASA for 72 hours is likely to ensure substantial (if not complete) recovery of platelet function. Second, in the ISIS-2 Trial that randomized 17,187 patients to ASA or placebo in the acute MI setting, they included patients who were taking ASA chronically even if they took ASA on the day of their MI.[72] There were 2266 patients in this subgroup, and it demonstrated a statistically significant reduction in vascular death, consistent with the overall finding.[72]

7.0 PLAN TO MINIMIZE RISKS AND MONITORING FOR AND APPROACH TO POTENTIAL PROBLEMS

Perioperative ASA may increase the risk of major bleeding. To minimize this risk, we are excluding patients with active peptic ulcer disease and patients undergoing intracranial or retinal surgery. Further, we are using low-dose ASA in POISE-2.

Multivariable analyses suggested that clinically important hypotension primarily caused the negative outcomes of death and stroke in POISE-1. Perioperative clonidine may result in clinically important hypotension, but we have incorporated many design features into POISE-2 to minimize this risk. In POISE-2 we require patients to have a SBP $\geq$ 105 mm Hg and a heart rate $\geq$ 55 beats per minute (bpm) to be eligible for the trial and to receive the clonidine study drug, whereas in POISE-1 patients received the study drug if they had a SBP $\geq$ 100 mg Hg and their heart rate was $\geq$ 50 bpm. We have also mandated more frequent monitoring of blood pressure and heart rate in POISE-2 (i.e., prior to study drug administration, 1 hour after administration, and QID while in hospital) compared to POISE-1 (i.e., we only required monitoring prior to and during administration of metoprolol). In POISE-2 we are using low-dose clonidine (i.e., < 0.3 mg/day) starting 2-4 hours prior to surgery and continuing for 72 hours after surgery. The POISE-2 Pilot and our systematic review provide encouraging evidence that low-dose clonidine does not induce clinically important hypotension.

Because non-study antihypertensive medications can also exacerbate the risk of clinically important hypotension we encourage the following approach for all POISE-2 patients:

1. Study personnel will tell POISE-2 patients who are taking an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) to not take any of these medications on the day of surgery. We have conducted a meta-analysis of the 3 RCTs that have randomized patients to either hold or continue their ACE-I or ARB on the day of surgery, Table 6.[105-107] Patients taking their ACE-I or ARB on the day of surgery demonstrated a higher risk of hypotension (RR 7.7; 95% CI, 3.4-17.2, I^2 0%).
2. Study personnel will tell POISE-2 patients who are taking any other anti-hypertensive medications to not take these medications on the morning of surgery but to take these medications to the preoperative surgical holding area.
3. In the preoperative surgical holding area (goal 2-4 hours prior to surgery) study personnel will check the patient's vital signs. Study personnel will convey the patient's hemodynamics to the anesthesiologist or surgeon managing the case and ask if they want the patient to receive any of their non-ACE-I/ARB anti-hypertensive medications and if yes at what dose.

Decisions regarding holding or discontinuing either study drug rest with the attending physician. If a patient develops clinically important hypotension or bradycardia, study personnel will encourage the attending physician to consider fluid resuscitation, administering an inotrope or vasopressor, withholding the patient's non-study antihypertensive medication(s), or if applicable changing the patient's epidural infusion rate. If the patient's clinically important hypotension or bradycardia persists despite these measures, study personnel will encourage removal of the patient's clonidine patch. If a patient without a pacemaker develops asystole or a second or third degree heart block that does not quickly resolve and for which there is not a likely alternative explanation (e.g., metabolic abnormality) then study personnel will recommend that removal of the patient's clonidine patch.

If a patient experiences a life-threatening or major bleed, study personnel will recommend that the patient have their ASA trial medication held until the bleeding is stabilized. After the bleeding

episode has resolved study personnel will ask the attending physician if they feel it is safe to restart the ASA trial medication.

8.0 OTHER MANAGEMENT AT THE DISCRETION OF THE ATTENDING PHYSICIAN

All aspects of the patient's management are at the discretion of the attending physician. This includes all decisions on antiplatelet, anticoagulation, and anti-ischemic therapies. We will encourage physicians not to prescribe an alpha-2 agonist during the first 4 days after surgery while the clonidine trial medication is likely having an effect (i.e., the first 3 days during administration of the clonidine patch and the 24 hours after removal of the patch when physiological effects are likely to persist). We will also encourage physicians not to prescribe antiplatelet therapy during the initial 7 days after surgery to patients in the ASA Continuation Stratum and for the initial 30 days after surgery to patients in the ASA Starting Stratum (i.e., periods when the patients will receive the ASA trial medication). If specific indications for an alpha-2 agonist or antiplatelet drug arise, the relevant trial medication can be stopped while an open label alpha-2 agonist or ASA is administered. Study personnel will document any open label usage of an alpha-2 agonist or ASA during the first 30 days after surgery.

9.0 FOLLOW-UP

Patient's will have a troponin (or CK-MB if troponin is not available) drawn 6 to 12 hours after surgery and on the first, second, and third days after surgery. Standard orders will dictate these tests are drawn. Standard orders will also ensure patients have an electrocardiogram (ECG) immediately after an elevated troponin is detected. Study personnel will recommend and attempt to obtain an echocardiogram on patients with an elevated troponin but no ECG changes, ischemic symptoms, or pulmonary edema.

Research personnel will follow patients throughout their time in hospital evaluating the patients and reviewing their medical records ensuring trial orders are followed and noting any outcomes. The research personnel will contact patients by phone at 30 days and 1 year after randomization. If patients indicate that they have experienced an outcome, study personnel will obtain the appropriate documentation.

10.0 TRIAL OUTCOMES

The overall primary outcome of the POISE-2 Trial is a composite of all-cause mortality and nonfatal MI at 30 days after randomization. Individual secondary outcomes at 30 days after randomization include: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis. In each ASA stratum, we will also assess a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization. The safety outcomes in the ASA trial are stroke, congestive heart failure, life-threatening bleeding, and major bleeding at 30 days after randomization. The safety outcomes in the clonidine trial are stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure at 30 days after randomization.

For the 1-year follow-up our primary outcome is all-cause mortality and nonfatal MI. Secondary 1-year follow-up outcomes include each of the following individual outcomes: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, and rehospitalization for vascular reason. Appendix provides definitions for all outcomes.

11.0 ADJUDICATION OF TRIAL OUTCOMES

Outcome adjudicators (a committee of clinicians with expertise in perioperative outcomes) who are blinded to treatment allocation will adjudicate the following outcomes: death (vascular versus non-vascular), MI, nonfatal cardiac arrest, pulmonary emboli, deep venous thrombosis, stroke, life-

threatening bleeding, and major bleeding. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Drs. Gordon Guyatt and Ganesan Karthikeyan will Co-chair the Adjudication Committee.

12.0 DATA ANALYSES

We will analyze patients in the treatment group to which they are allocated, according to the intention-to-treat principle. We will compare patients allocated to clonidine with patients allocated to clonidine placebo, and we will compare patients allocated to ASA with patients allocated to ASA placebo.

12.1 Main Analyses

We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will use log-rank tests to compare the rate of occurrence of the primary outcome between the ASA versus ASA placebo group and separately the clonidine versus the clonidine placebo group. We will use Cox proportional hazards models to estimate the effect of clonidine, and of ASA, on the hazard ratio for the primary and secondary outcomes (with stratification according to whether treatment included the other agent). We will calculate the hazard ratios and their associated 95% confidence intervals. We will infer statistical significance if the computed 2-sided p-value is < 0.05. We anticipate that the treatment effect of clonidine and ASA, if present, will act independently, but we will, however, evaluate the possibility of synergism or antagonism by formally testing the interaction term in a Cox model.

12.2 Subgroup Analyses

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the clonidine subgroup analyses (i.e. neuro-axial blockade, vascular surgery) and the ASA subgroup analyses (i.e. ASA stratum, diabetes, creatinine > 175 μmol/L). We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $P < 0.05$.

12.3 Interim Analyses

Three interim efficacy analyses based on the primary outcome will occur when 25%, 50% and 75% of the 30-day data are available. The External Safety and Efficacy and Monitoring Committee (ESEMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) ($\alpha = 0.0001$) for analyses in the first half of the trial and 3 SDs ($\alpha = 0.00047$) for all analyses in the second half.[108 109] For a finding in favor of 1 or both active treatments to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 3 or more months apart. The α-level for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation with subsequent analyses.

The ESEMC will monitor for an adverse impact of clonidine on stroke or mortality, or ASA on stroke, life-threatening bleeding, or mortality. For these analyses, a 3 SDs excess in the first half and a 2.6 SDs excess in the second half of the trial would trigger discussions about stopping for harm.

At any time during the trial if safety concerns arise the ESEMC chairperson will assemble a formal meeting of the full committee. The ESEMC will make their recommendations to the Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered the ESEMC will invite the Operations Committee to explore all possibilities before a decision is made.

13.0 REPORTING SERIOUS ADVERSE EVENTS

We define serious adverse events (SAEs) as those which are fatal, life threatening or fulfill a definition of being clinically important. Efficacy or safety outcomes will not be considered as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition. All events considered as part of the primary, secondary, or safety events (as outlined in section 10.0), should be reported on the appropriate page(s) in the case report forms (CRFs) but not as

an SAE, unless considered exceptional in this medical condition.

In this trial, the following events (all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, congestive heart failure, stroke, rehospitalization for vascular reasons, life-threatening bleeding, major bleeding, clinically important hypotension, and clinically important bradycardia are considered related to the underlying cardiovascular disease and are not considered an SAE. These events will not be considered unexpected unless their course, severity or other specific features are such that the investigator, according to his/her best medical judgment, considers these events as exceptional in the context of the patient's medical condition.

Only unexpected and not previously described serious adverse events that are believed with a reasonable level of certainty to be associated with the trial medication need to be reported immediately (i.e. within 24 hours of knowledge of the event) to the Central Coordinating Office. For such events research personnel should complete an SAE CRF and immediately enter it into the iDatafax Database System or fax it to the Project Office, who will then inform the sponsor and the regulatory bodies.

14.0 TRIAL MANAGEMENT

14.1 What are the Arrangements for the Day to Day Management of the Trial?

Figure 2 illustrates the organizational structure of POISE-2 and Table 7 describes the trial timetable. The Population Health Research Institute (PHRI) Project Office, McMaster University, Hamilton, Canada is the coordinating center for this trial and is primarily responsible for the development of the trial protocol, organization of the trial, development of the randomization scheme, the trial database, data internal consistency checks, data analyses, and coordination of the trial centres. The POISE-2 Principal Investigator, Project Officer, Project Manager, and Coordinator are responsible for the activities of the Project Office. Dr. P.J. Devereaux is the Principal Investigator (PI), and he is responsible for the overall supervision of the trial. Dr. Devereaux was the Co-PI of the largest perioperative cardiac RCT (POISE-1), and he is the PI of the largest international perioperative vascular complications prospective cohort study (VISION). Dr. Marko Mrkobrada is the Project Officer, and he is responsible for providing clinical support to the trial and providing guidance to the Trial Coordinator.

The Project Manager (Ms. Susan Chrolavicius) has extensive experience running large cardiovascular trials, and she will oversee the Trial Coordinator (Ms. Andrea Robinson) who has experience in large international trials. The POISE-2 Trial Coordinator is responsible for the daily conduct of the trial including supervising the data management assistant (who is responsible for data validation and quality); supplying centres with POISE-2 posters, pocket cards, and a detailed Manual of Operations that will outline each step of the protocol; producing and presenting to the Principal Investigator, Project Officer, and Project Manager: monthly reports on screening, patient follow-up, data transmission, consistency and thoroughness of data collection, and event rates; transmitting these reports to sites; develop and transmit to all trial investigators and research personnel weekly enrolment reports; monitoring and contacting any centres with high rates of eligible but not enrolled patients to discuss procedures and establish solutions to problems; communication with investigators and research personnel regarding protocol and other procedural questions; answer the project office's toll free phone number that investigators and trial personnel can call to resolve any problems or questions that arise; coordination of supplying study drug and aids; writing and distributing quarterly trial newsletters; maintenance of required documentation for regulatory agencies; review of all events prior to adjudication, compilation of all the records required for the adjudication process, coordination of the adjudication process, maintenance of the adjudication database; preparation of presentations to the trial committees; organization of Investigator Meetings, Project Office Operations Committee meetings, International Operations Committee meetings, Steering Committee meetings, Adjudication Committee meetings, External Safety and Efficacy and Monitoring Committee, Sub-study and Publications Committee meetings, and weekly project office meetings with the Principal Investigator and Project

Officer.

14.2 Project Office Operations Committee and International Operations Committee

The project office is responsible for the day-to-day trial management and will report directly to the Project Office Operations Committee. This committee will consist of P.J. Devereaux, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Salim Yusuf, Gordon Guyatt, Janice Pogue, and Kristian Thorlund. The Project Office Operations Committee will meet monthly to review trial progress and all pertinent issues related to the conduct of POISE-2. The Project Office Operations Committee will report directly to the International Operations Committee. This committee will include broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the International Operations Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Kristian Thorlund, Ganesan Karthikeyan, Pablo Alonso-Coello, Colin Baigent, Otavio Berwanger, Bruce Biccard, Matthew Chan, Clara Chow, Christian Gluud, Claes Held, Michael Jacka, Giovanni Landoni, Kate Leslie, German Malaga, Paul Myles, Martin O'Donnell, Prem Pais, Dan Sessler, Wojciech Szczeklik, Juan Carlos Villar, Chew Wang, Jorn Wetterslev, and Denis Xavier. The International Operations Committee will hold confererence calls biannually and will review the progress of the trial, international POISE-2 issues, and strategies to ensure the successful conduct and completion of POISE-2.

14.3 The Steering Committee and National Principal Investigators

The International Operations Committee will report to the Steering Committee. We will hold an on-site meeting of the Steering Committee twice during the trial and annual conference calls. At these meetings the International Operations Committee will report to the Steering Committee regarding the overall progress of the trial and plans to ensure successful conduct and completion of POISE-2. For each participating country in POISE-2, the Project Office Operations Committee will appoint a member of the Steering Committee to act as the National Principal Investigator. At the Steering Committee Meetings each National Principal Investigator will provide a brief report to the Steering Committee regarding the country's progress in POISE-2, goals for the coming year, and any issues that require input. The Steering Committee will include a broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the Steering Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Kristian Thorlund, Ganesan Karthikeyan, Pablo Alonso-Coello, Sonia Anand, Andrew Auerbach, Colin Baigent, Scott Beattie, Otavio Berwanger, Mohit Bhandari, Bruce Biccard, Norm Buckley, Matthew Chan, Clara Chow, Deborah Cook, Jim Douketis, John Eikelboom, Jim Eisenach, Amit Garg, Bill Ghali, Christian Gluud, Michelle Graham, Robert Hart, Claes Held, Michael Hill, Michael Jacka, Eric Jacobsohn, Clive Kearon, Andre Lamy, Giovanni Landoni, Kate Leslie, German Malaga, Finlay McAlister, Paul Myles, Peter Nagele, Martin O'Donnell, Prem Pais, Joel Parlow, Dan Sessler, Thomas Schricker, Marko Simunovic, Sadeesh Srinathan, Wojciech Szczeklik, Kevin Teoh, David Torres Perez, Gerard Urrutia, Juan Carlos Villar, Michael Walsh, Chew Wang, Jørn Wetterslev, Richard Whitlock, Duminda Wijeysundera, Denis Xavier, and Homer Yang.

14.4 Centre Principal Investigators

All participating centres will have a Centre Principal Investigator, and this individual is responsible for: (1) obtaining ethics approval from the institutional review board or the ethics board and forwarding this to the Project Office; (2) ensuring study approval is obtained before recruitment starts; (3) ensuring the protocol is followed; (4) ensuring all physicians and nurses involved in the perioperative care of patients undergoing non-cardiac surgery are aware and informed about the POISE-2 Trial (this will involve organizing and presenting educational in-services about the trial and distributing posters and pocket protocols); (5) ensuring that all surgical patients are screened for the

trial; (6) ensuring that all enrolled patients have their troponins obtained and ECGs and echocardiograms when appropriate; (7) ensuring that all enrolled patients are followed appropriately; (8) ensuring that all Case Report Forms (CRFs) are promptly and accurately completed and submitted to the Project Office, and that all inquiries from the Project Office regarding patient forms or other matters are addressed promptly; (9) ensuring that a simple screening log is kept of all eligible noncardiac surgery patients who are not enrolled in the POISE-2 Trial and the primary reason they were not enrolled; (10) ensuring they maintain for at least 10 years after the publication of the main results, the list of patient identification numbers and patient names to enable identification of hospital records at a later date.

14.5 Sub-study and Publication Committee

The Project Office Operations Committee will appoint members to a Sub-study and Publication Committee. This committee will create guidelines for sub-studies and publications related to POISE-2. We will publish the main POISE-2 manuscript under group authorship, with the roles of all investigators acknowledged in an appendix. Subsequent publications will be authored by specific individuals on behalf of the POISE-2 Investigators. Individuals selected to lead the writing of these subsequent publications will depend on their role in and contribution to POISE-2, scientific interest, and scientific expertise.

15.0 OTHER CONSIDERATIONS

15.1 Ensuring Data Quality

Several procedures will ensure data quality including: 1) all research personnel will undergo a training session prior to trial commencement to ensure consistency in trial procedures including data collection and reporting; 2) all centres will have a detailed trial Manual of Operations that will outline each step of the protocol; 3) investigators can use a toll free phone number to a help line at the project office to resolve any problems or questions that arise; 4) the project office personnel will evaluate all data as soon as it is received and quality control checks will identify any errors or omissions; then the project office personnel will notify the sender of any such issues via secure internet, email, telephone, or visit if necessary; 5) the project office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, consistency, thoroughness, and completeness of data collection (e.g., troponin measurements), and event rates, and they will immediately address any identified issues; and 6) the programmer will create internal validity and range checks using the Clinical iDataFax Database System which will identify any errors or omissions and notify the sender and data management assistants of any such issues; 7) the data management assistants will undertake multi-level data validation of the trial Case Report Forms; 8) the Trial Coordinator will (A) send investigators regular quality control reports; (B) obtain from the trial statistician and present to the principal investigator bi-monthly reports on internal validity and range checks using the iDataFax Database System; 9) the study statistician will undertake statistical monitoring every 6 months to identify outliers through (A) comparing centre and data collector variables (e.g., rates of reported primary outcomes), and (B) multivariate tests to examine associations of patient variables across hospitals and data collectors, and 10) we will undertake on-site monitoring at sites based upon the number of patients recruited and for any sites that stand out on statistical monitoring and an experienced monitor will audit a random selection of trial patients with and without a submitted primary outcome case report form.

15.2 Confidentiality and Blinding

All patient information will be stored on a high security computer system and kept strictly confidential. Only the ESEMC and the study statistician who reports to the ESEMC will be aware of the unblinded data until the trial is completed or a recommendation is made to terminate the trial.

15.3 Unblinding

Legitimate situations such as a large overdose of the study drug may require unblinding. We will avoid unblinding when appropriate through use of the following strategy. Prior to unblinding the attending physician will have to complete a detailed checklist to document the reason for unblinding and

whether alternatives have been explored. Frequently stopping the study medication, skipping a dose, or giving open label medication will be adequate for the management of most situations. We recommend that all unblinding decisions be made jointly with the Project Office. If after these steps the local study investigator believes emergency unblinding is essential for the patient's management then it can be undertaken.

15.4 Patients Stopping Their Study Medication(s)

Patients can choose to stop their study medication(s) at any time during the course of the trial. Study Personnel will follow patients who make this decision in the same way that they follow all other trial participants. If a patient stops their study medication(s), the Centre Principal Investigator will discuss this decision with the patient. If after this discussion the trial participant decides they want to resume the trial medication(s) the Centre Principal Investigator will re-initiate the study medication(s) if they feel the study medication(s) can be safely restarted.

16.0 POTENTIAL SIGNIFICANCE OF POISE-2

Over 200 million adults annually undergo major noncardiac surgery and 3-5 million will suffer a major vascular complication. POISE-2 will answer two crucial management questions and influence future perioperative practices around the world.

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TABLE 1: POISE-2 Pilot results*

Outcome	Clonidine (N=30)	Clonidine Placebo (N=30)	ASA (N=30)	ASA Placebo (N=30)
Death	0	0	0	0
MI	0	2	1	1
Stroke	1	0	1	0
Cardiac arrest	0	1	1	0
Clinically significant hypotension	6	10	9	7
Clinically significant bradycardia	4	2	6	2
Bleeding	8	10	9	9
CHF	0	1	1	0

* Data from the first 60 patients included in the pilot; CHF = congestive heart failure

TABLE 2: Meta-analysis of trials evaluating perioperative clonidine

Outcome	Trial	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	Wallace[31]	1/125	4/65	0.13	0.01 to 1.14	
	Quintin[33]	0/11	1/10	0.31	0.01 to 6.74	
	Stuhmeier[55]	1/145	2/152	0.52	0.05 to 5.72	
	Total	**2/311**	**8/258**	**0.27**	**0.07 to 0.99**	**0%**
Myocardial infarction						
	Ellis[30]	0/30	2/31	0.21	0.01 to 4.13	
	Wallace[31]	5/125	3/65	0.87	0.21 to 3.51	
	Stuhmeier[55]	0/145	4/152	0.12	0.01 to 2.14	
	POISE-2 Pilot*	0/30	2/30	0.20	0.01 to 4.00	
	Total	**5/330**	**11/278**	**0.45**	**0.15 to 1.33**	**0%**
Nonfatal cardiac arrest						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	

	Total	**0/60**	**2/61**	**0.34**	**0.04 to 3.17**	**0%**
Stroke					
	Wallace[31]	1/125	0/65	1.57	0.06 to 38.04	
	Schneemilch[57]	0/40	5/40	0.09	0.01 to 1.59	
	POISE-2 Pilot*	1/30	0/30	3.00	0.13 to 70.83	
	Total	**2/195**	**5/135**	**0.69**	**0.07 to 6.37**	**37%**
Congestive heart failure					
	Ellis[30]	4/30	5/31	0.83	0.25 to 2.79	
	Wallace[31]	0/125	2/65	0.10	0.01 to 2.15	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	
	Total	**4/185**	**8/126**	**0.58**	**0.20 to 1.67**	**0%**
Myocardial ischemia					
	Ellis[30]	7/30	8/31	0.90	0.37 to 2.18	
	Wallace[31]	18/125	20/65	0.47	0.27 to 0.82	
	Morris[46]	4/21	4/18	0.86	0.25 to 2.95	
	Pawlik[54]	0/15	1/15	0.33	0.01 to 7.58	
	Stuhmeier[55]	35/145	59/152	0.62	0.44 to 0.88	
	Lipszyc[58]	8/20	5/20	1.60	0.63 to 4.05	

Matot[59]	0/18	2/18	0.20	0.01 to 3.89	
Total	**72/374**	**99/319**	**0.66**	**0.49 to 0.89**	**8%**

* = POISE-2 Pilot results after recruitment of 60 patients

TABLE 3: Meta-analysis of perioperative clonidine trials, clinically important hypotension results

Outcome and Subgroup	Trial	Outcome definition	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Clinically important hypotension							
Low-dose clonidine (< 0.3mg/day)							
	Nader[37]	MAP 20% lower than baseline BP	2/7	2/8	1.14	0.21 to 6.11	
	Lemes[44]	MAP < 60 mmHg or 30% lower than baseline BP	1/33	0/35	3.18	0.13 to 75.33	
	Mayson[45]	SBP 25% lower than baseline BP	18/24	13/19	1.10	0.75 to 1.61	
	Morris[46]	MAP 20% lower than baseline BP	5/21	3/18	1.43	0.40 to 5.17	
	Sia[47]	SBP 20% lower than baseline BP	4/50	3/50	1.33	0.31 to 5.65	
	Stapelfeldt[48]	SBP < 90 mmHg	15/17	12/17	1.25	0.88 to 1.78	
	Stuhmeier[55]	MAP < 70 mmHg	20/145	26/152	0.81	0.47-1.38	
	Schneemilch[57]	MAP 20% lower than basline BP and treated with cafedrine/theoadrenaline	19/40	5/40	3.80	1.57 to 9.18	
	Fehr[60]	MAP < 50mmHg or >20% drop from pre-induction value	10/25	10/25	1.00	0.51 to 1.97	
	Rhee[61]	MAP 30% lower than baseline BP	5/52	1/26	2.50	0.31 to 20.31	

	Vanderstappen[62]	MAP 20% lower than preinduction value treated with ephedrine	4/140	2/140	2.00	0.37-10.74	
	Watanabe[63]	SBP < 90mmHg	8/22	4/20	1.82	0.65-5.12	
	POISE-2 Pilot*	SBP < 90 mm Hg that required an intra-aortic balloon pump, inotropic agent, fluid resuscitation, or study drug discontinuation	6/30	10/30	0.60	0.25 to 1.44	
	Subtotal		**117/606**	**91/580**	**1.19**	**0.95 to 1.49**	**12%**
High-dose clonidine (≥ 0.3mg/day)							
	Ellis[30]	SBP < 90 mmHg, unresponsive to fluid challenge	2/30	3/31	0.69	0.12 to 3.84	
	Wallace[31]	SBP < 80mmHg lasting ≥ 5 minutes	24/125	11/65	1.13	0.59-2.17	
	Quintin[33]	DBP < 90mmHg lasting more than 3 minutes intraoperatively or more than 5 minutes postoperatively	5/11	2/10	2.27	0.56 to 9.20	
	Pluskwa[40]	SBP < 100 mmHg lasting more than 3 minutes	12/14	8/15	1.61	0.96 to 2.70	
	Owen[49]	MAP 20% lower than baseline BP	14/15	4/14	3.27	1.41 to 7.56	
	Park[50]	SBP < 90 mmHg	8/22	2/22	4.00	0.95 to 16.75	
	Parlow[51]	SBP < 90 mmHg	2/10	0/10	5.00	0.27 to 92.62	
	Takahasi[52]	SBP < 80mmHg	17/21	5/17	2.75	1.28 to 5.92	

	Matot[59]	Intraprocedural drop in SBP more than 30% from preinduction value or absolute SBP < 90mmHg	2/18	0/18	5.00	0.26 to 97.37	
	Bernard[64]	MAP < 60mmHg	2/16	0/16	5.00	0.26 to 96.59	
	Bernard[65]	MAP $\leq$ 60mmHg	3/25	0/25	7.00	0.38 to 128.87	
	Sarkar[66]	SBP < 80mmHg and treated with ephedrine	2/22	1/21	1.91	0.19 to 19.52	
	Wright[67]	SBP < 80mmHg	14/30	0/30	29.00	1.81-465.07	
	Subtotal		**107/359**	**36/294**	**2.13**	**1.47 to 3.09**	**18%**
All trials (i.e., both low and high-dose)							
	Total		**231/1031**	**132/941**	**1.51**	**1.20 to 1.91**	**31%**

OR = odds ratio; SBP = systolic blood pressure; MAP = mean arterial blood pressure; BP = blood pressure; DBP = diastolic blood pressure; * = POISE-2 Pilot results after recruitment of 60 patients

TABLE 4: Meta-analysis of perioperative ASA trials

Outcome	Trial	ASA group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Wood[78]	2/9	2/9	1.00	0.18 to 5.63	
	Goldman[79]	0/22	2/31	0.28	0.01 to 5.53	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	4/32	11/34	0.39	0.14 to 1.09	
	McCollum[82]	40/286	46/263	0.80	0.54 to 1.18	
	Lindblad[83]	1/117	5/115	0.20	0.02 to 1.66	
	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	456/8726	472/8718	0.97	0.85 to 1.09	
	Total	**508/9251**	**538/9229**	**0.85**	**0.63 to 1.14**	**24%**
Vascular mortality						
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	1/32	10/34	0.11	0.01 to 0.78	
	McCollum[82]	15/286	31/263	0.44	0.25 to 0.81	
	Lindblad[83]	0/117	5/115	0.09	0.00 to 1.60	

	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	243/8726	263/8718	0.92	0.78 to 1.10	
	Total	**264/9229**	**310/9198**	**0.59**	**0.28 to 1.25**	**61%**
Nonfatal myocardial infarction						
	McCollum[82]	14/286	14/263	0.92	0.45 to 1.89	
	Nielsen[84]	0/26	1/27	0.35	0.01 to 8.12	
	PEP Trial[85]	43/8726	27/8718	1.59	0.98 to 2.57	
	POISE-2 Pilot	1/31	1/29	0.94	0.06 to 14.27	
	Total	**58/9069**	**43/9037**	**1.31**	**0.88 to 1.94**	**0%**
Nonfatal stroke						
	Findlay[86]	0/10	2/12	0.24	0.01 to 4.42	
	Kretschmer[81]	1/32	2/34	0.53	0.05 to 5.58	
	McCollum[82]	13/286	17/263	0.70	0.35 to 1.42	
	Lindblad[83]	5/117	7/115	0.70	0.23 to 2.15	
	PEP Trial[85]	37/8726	34/8718	1.09	0.68 to 1.73	
	Tytgat[87]	3/50	3/50	1.00	0.21 to 4.72	
	POISE-2 Pilot	1/31	0/29	2.81	0.12 to 66.40	
	Total	**60/9252**	**65/9221**	**0.91**	**0.64 to 1.29**	**0%**

Nonfatal pulmonary embolism					
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24
	Renney[88]	1/85	1/75	0.88	0.06 to 13.86
	Harris[89]	0/44	1/51	0.39	0.02 to 9.22
	McKenna[90]	1/9	3/12	0.44	0.05 to 3.60
	Alfaro[91]	0/30	1/30	0.33	0.01 to 7.87
	PEP Trial[85]	36/8726	46/8718	0.78	0.51 to 1.21
	Total	**38/8903**	**53/8895**	**0.74**	**0.49 to 1.11** **0%**
Major bleeding					
	McKenna[90]	1/9	0/12	3.90	0.18 to 85.93
	Green[92]	1/75	0/88	3.51	0.15 to 84.98
	McCollum[82]	18/286	9/263	1.84	0.84 to 4.02
	Lindblad[83]	2/117	1/115	1.97	0.18 to 21.38
	Nielsen[84]	1/26	2/27	0.52	0.05 to 5.39
	PEP Trial[85]	182/8726	122/8718	1.49	1.19 to 1.87
	POISE-2 pilot	9/31	9/29	0.94	0.43 to 2.03
	Total	**214/9270**	**143/9252**	**1.47**	**1.19 to 1.80** **0%**

TABLE 5: Sample size calculations

Primary Outcome (all-cause mortality or nonfatal MI at 30 days)			Power (2-sided $\alpha = 0.05$)		
Control event rate	**% of patients not receiving or prematurely discontinuing study drug ***	**Hazard Ratio**	**N = 9000**	**N=10,000**	**N=11,000**
5.6%	10%	0.75	76.9%	81.1%	84.6%
6.1%	10%	0.75	80.3%	84.3%	87.5%

* Based on POISE-2 Pilot among patients discontinuing clonidine prematurely the discontinuation rate was 80% on the first day and 20% on the second day.

TABLE 6: Meta-analysis of trials evaluating preoperative management of ACE-I and ARB medications

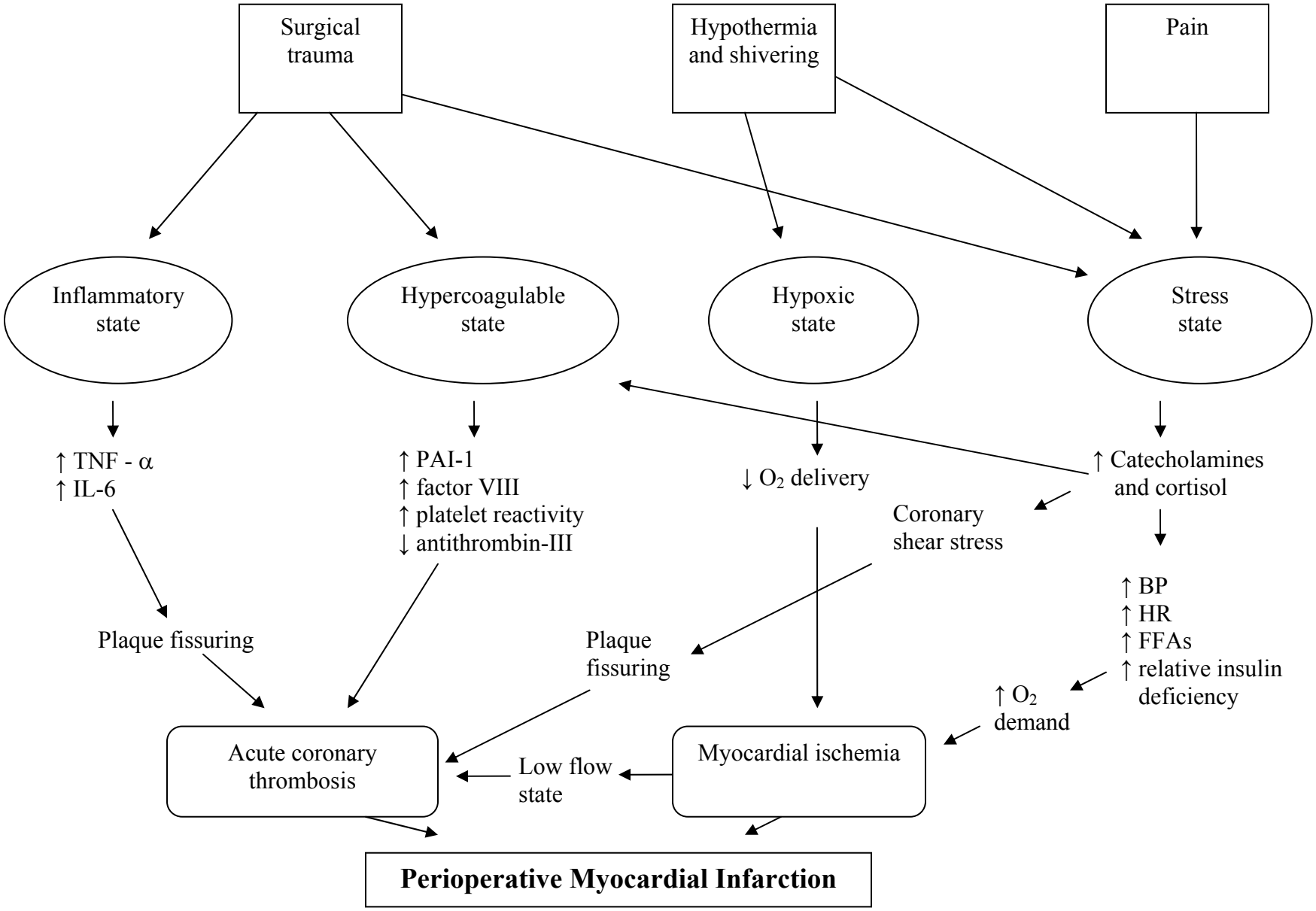
Hypotension						
Trial	**Trial Definition of Intraoperative Hypotension**	**ACE-I/ARB in Immediate Preoperative Period n/N**	**Control group n/N**	**Relative risk**	**95% CI**	**I^2**
Schirmer[105]	Mean arterial blood pressure <60 mmHg	17/50	5/50	4.6	1.6 to 13.8	
Bertrand[106]	Systolic blood pressure <80 mmHg longer then 1 minute	19/19	12/18	20.3	1.05 to 392.5	
Coriat[107]	Systolic blood pressure <90 mmHg	16/21	6/30	12.8	3.34 to 49.1	
Total		**52/90**	**23/98**	**7.7**	**3.4 to 17.2**	**0%**

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

TABLE 7: POISE-2 trial timeline

Phase	Time (months)	Tasks
1 (planning)	6	1. Meeting of investigators for discussion of protocol and finalization of procedures 2. Translation of the protocol into non-English languages 3. Development of all study aids 4. Study approval by local ethics committee 5. Health Canada Approval and regulatory approval in other countries 6. Drug packaging and kit preparation, 7. Development of randomization sequence 8. Shipping trial materials 9. Ensure local teams are ready to start recruitment to avoid delays during recruitment phase
2 (recruitment)	36	Recruitment of 10,000 patients
3 (short-term follow-up)	1	All patients are actively followed for 1 month including all patients enrolled at the end of the recruitment phase
4 (completion of short-term study)	6	1. Data clean-up 2. Confirmation and classification of events 3. Data analysis 4. Publication of primary and secondary results
5 (long-term follow-up)	5	All patients are actively followed for 1 year.
6 (completion of long-term study)	6	1. Data analysis 2. Publication of primary and secondary results

FIGURE 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

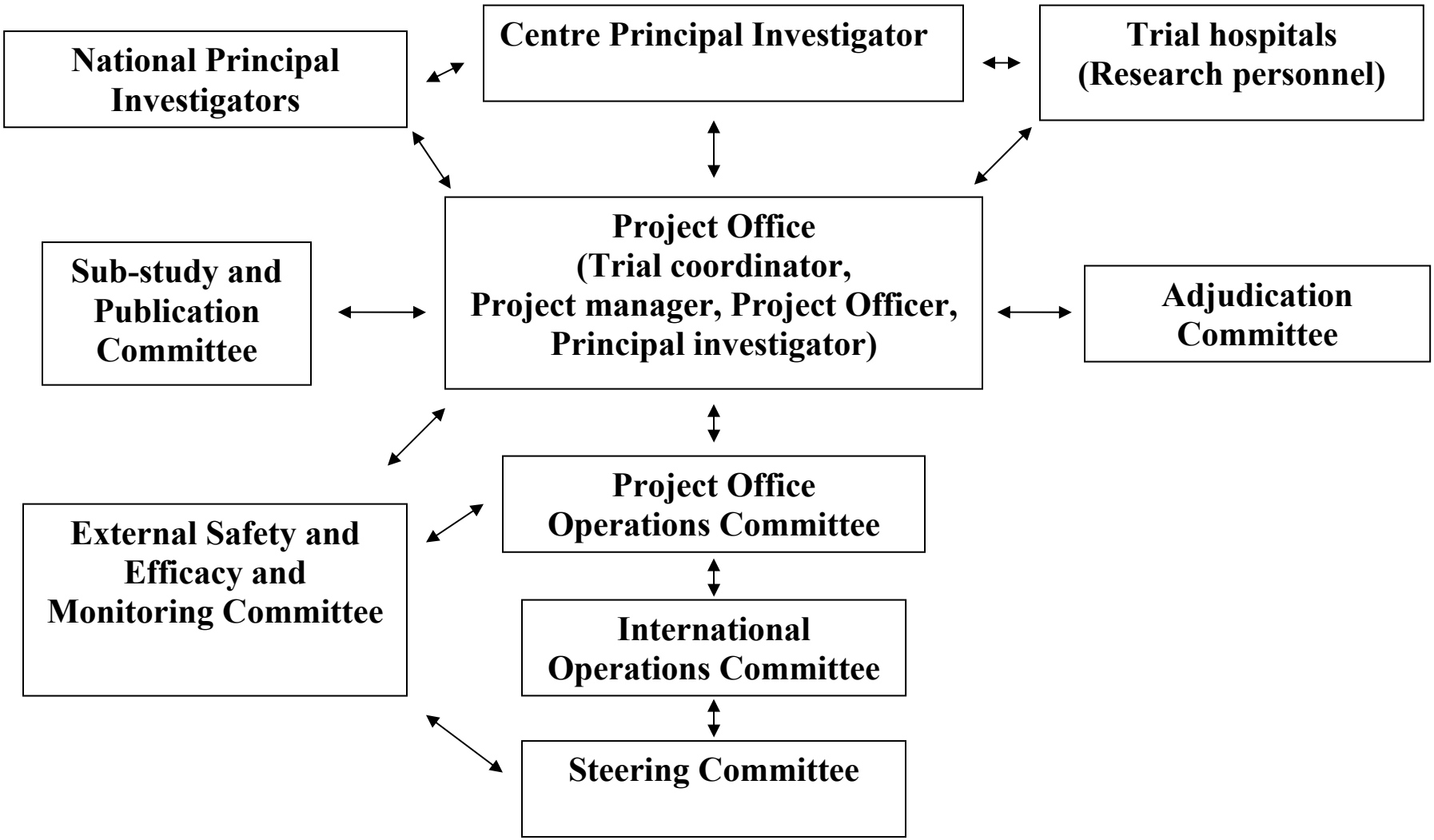


LEGEND

Figure 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

TNF-α = tumor necrosis factor α, IL-1 = interleukin-1, IL-6 = interleukin-6, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor -1, O_2 = oxygen, BP = blood pressure, HR = heart rate, FFAs = free fatty acids

FIGURE 2: POISE-2 Organizational Structure



APPENDIX: POISE-2 outcome definitions

1. Sub-classification of death

Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).

2.0 Myocardial infarction

The diagnosis of MI requires any one of the following criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also requires that 1 of the following must also exist:

    A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)

    B. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds

    C. ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads

    D. coronary artery intervention (i.e., PCI or CABG surgery)

    E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

2. Pathologic findings of an acute or healing myocardial infarction
3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

3. Nonfatal cardiac arrest

Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

4. Cardiac Revascularization Procedures

Cardiac revascularization procedures include PCI and CABG surgery.

5. Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.

6. Pulmonary embolus (PE)

The diagnosis of PE requires any one of the following:

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:

    A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan

    B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

7. Deep venous thrombosis (DVT) of leg or arm

The diagnosis of DVT requires any one of the following:

1. A persistent intraluminal filling defect on contrast venography
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography

3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

8. New Clinically Important Atrial Fibrillation

New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

9. Re-hospitalization for Vascular Reasons

Re-hospitalization for vascular reasons is defined as re-hospitalization for MI, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolus, any vascular surgery, or bleeding.

10. Life-threatening bleeding

Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

11. Major bleeding

Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" above, and results in a postoperative hemoglobin ≤ 70 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in a hemoglobin drop of ≥ 50 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in the patient receiving a transfusion of ≥ 4 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); OR is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

12. Clinically important hypotension

Clinically important hypotension is defined as a systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.

13. Clinically important bradycardia

Clinically important bradycardia is defined as a heart rate < 55 beats per minute requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.

15. Congestive heart failure

The definition of congestive heart failure requires at least one of the following clinical signs (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) **and** at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

16. New acute renal failure requiring dialysis

Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

POISE-2 Trial

PeriOperative ISchemic Evaluation-2 Trial

A large, international, placebo-controlled, factorial trial to assess the impact of clonidine and acetyl-salicylic acid (ASA) in patients undergoing noncardiac surgery who are at risk of a perioperative cardiovascular event

An International Collaborative Initiative

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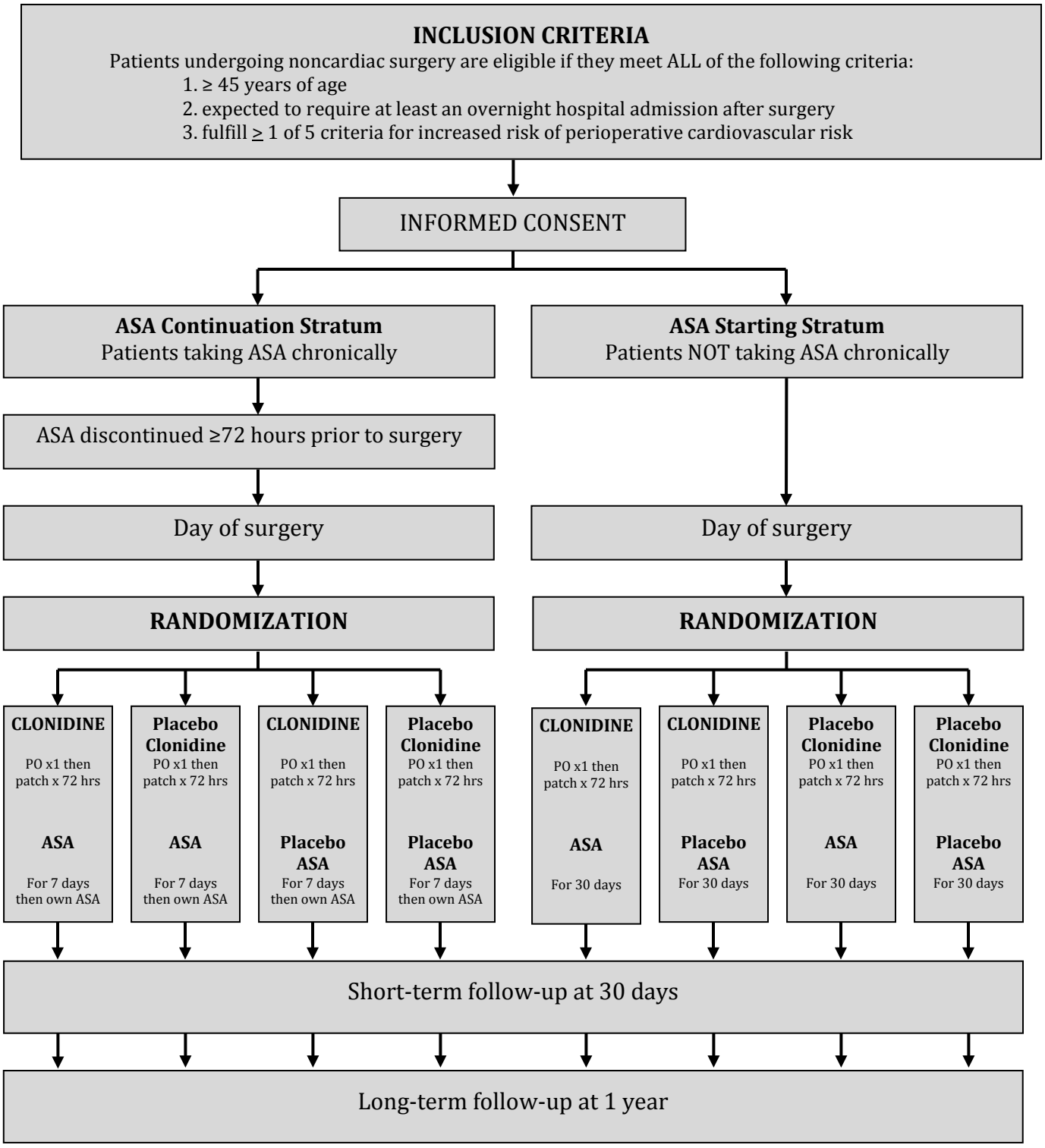
Version 4, April 6, 2011

Study Flow Chart



Title	**The PeriOperative Ischemic Evaluation-2 (POISE-2) Trial**
Project Office	POISE-2 Project Office Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Room C1-231 Hamilton, Ontario, Canada L8L 2X2
Study Size	10,000 patients
Study Design	Multicentre, international, blinded, 2x2 factorial randomized controlled trial of acetyl-salicylic acid (ASA) and clonidine.
Primary Objective	To determine the impact of clonidine versus placebo and ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.
Secondary Objective	To determine the impact of clonidine and ASA on cardiovascular events at 30 days and 1 year after surgery.
Inclusion Criteria	Patients undergoing noncardiac surgery are eligible if they: 1. are $\geq$ 45 years of age; 2. are expected to require at least an overnight hospital admission after surgery; AND 3. fulfill one or more of the following 5 criteria A. history of coronary artery disease; B. history of peripheral vascular disease; C. history of stroke; D. undergoing major vascular surgery; OR E. any 3 of the following 9 criteria: undergoing major surgery (i.e. intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery), history of congestive heart failure, transient ischemic attack, diabetes and currently taking an oral hypoglycemic agent or insulin, age $\geq$ 70 years, hypertension, serum creatinine > 175 μmol/L (> 2.0 mg/dl), history of smoking within 2 years of surgery, undergoing urgent/emergent surgery
Treatment Regimen	**Clonidine:** 2-4 hours prior to surgery, patients will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The patch will be removed at 72 hours after surgery. **ASA Continuation Stratum (patients taking ASA chronically):** Patients will be randomized to continue ASA or withdraw ASA and take a placebo starting on the day of surgery. Patients will continue taking the ASA trial intervention until 7 days after surgery after which patients will restart taking their regular ASA. **ASA Starting Stratum (patients not taking ASA chronically):** Patients will be randomized to start ASA or placebo on the day of surgery and will continue taking the ASA trial intervention until 30 days after surgery.

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1.0 INTRODUCTION AND RATIONALE

During the last few decades, substantial advances in noncardiac surgery have improved disease treatment and patients' quality of life. As a result, the number of patients undergoing noncardiac surgery is growing. A recent study that used surgical data from 56 countries suggests that 200 million major noncardiac surgical procedures are undertaken annually around the world.[1,2]

Noncardiac surgery is associated with major vascular complications (i.e., vascular death, nonfatal myocardial infarction [MI], nonfatal cardiac arrest, and nonfatal stroke). Worldwide, approximately 3-5 million adult patients annually suffer a major perioperative vascular complication in the first 30 days after surgery,[2] a number similar to the annual global incidence of new patients acquiring human immunodeficiency virus (HIV).[3] There is not a single established effective and safe intervention to prevent major perioperative vascular complications.[4] The striking absence of prophylactic interventions reflects the paucity of large randomized controlled trials (RCTs) evaluating perioperative interventions. Major perioperative vascular complications are therefore a major neglected public health problem.

We recently completed the largest RCT focused on cardiovascular complications in noncardiac surgery (the PeriOperative ISchemic Evaluation-1 [POISE-1] Trial).[5] In POISE-1, we randomized 8,351 patients with, or at risk of, atherosclerotic disease from 190 hospitals in 23 countries to receive extended-release metoprolol succinate (metoprolol CR) or placebo starting 2-4 hours prior to surgery and continuing for 30 days. Metoprolol decreased the 30-day risk of MI (hazard ratio [HR], 0.73; 95% CI, 0.60-0.89) but increased the risk of death (HR, 1.33; 95% CI, 1.03-1.74) and stroke (HR, 2.17; 95% CI, 1.26-3.74). These harmful consequences, unanticipated prior to POISE-1, have influenced thinking in this area and highlight the importance and need for large RCTs in perioperative medicine.

There are encouraging laboratory, physiology, operative and non-operative data suggesting that perioperative low-dose clonidine and low-dose acetyl-salicylic acid (ASA) may prevent all-cause mortality and nonfatal MI without excessive risk of major bleeding and clinically important hypotension. We will undertake a large international factorial RCT to establish the effects of these 2 interventions in patients undergoing noncardiac surgery. We call this RCT the POISE-2 Trial.

1.1 Principal Research Question

What is the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery?

1.2 Need for POISE-2 Trial

1.2.1 Pathophysiology of perioperative MI

MI is the most common major perioperative vascular complication. In the placebo group of the POISE-1 Trial 1.4% of the patients suffered a vascular death, 0.5% suffered a stroke, 0.5% suffered a nonfatal cardiac arrest, and 5.7% suffered an MI in the first 30 days.[5] Perioperative MI carries a poor prognosis. In the POISE-1 Trial 11.6% of the patients suffering a perioperative MI died within the first 30 days, and both asymptomatic and symptomatic perioperative MIs were powerful independent predictors of death at 30 days (odds ratio [OR] 3.45; 95% CI, 2.20-5.41 and OR 3.31; 95% CI, 1.78-6.15, respectively).[5] Further, a meta-analysis of noncardiac surgery studies suggests that an elevated troponin after surgery is a strong independent predictor of mortality up to 1 year after surgery (OR 6.7; 95% CI, 4.1-10.9).[6] Insights from the pathophysiology of perioperative MI may inform the type of intervention that will prevent this event.

Rupture of atherosclerotic plaque with superimposed arterial thrombosis constitutes the underlying pathophysiology in the majority of non-operative MIs.[7] Among patients suffering a non-operative MI, 64-100% have coronary artery plaque fissuring and 65-95% have an acute luminal thrombus.[8-13]

1.2.1.1 Potential role of supply-demand mismatch in the pathophysiology of perioperative MI

In contrast to non-operative MI, myocardial oxygen supply-demand mismatch represents a commonly proposed mechanism of perioperative MI.[14] Patients undergoing major noncardiac surgery experience an increase in sympathetic output and hence a rise in catecholamines[15-17] that result in an increase in heart rate and hence myocardial oxygen demand.[15 16] Noncardiac surgery is also associated with hypothermia that leads to shivering, which increases myocardial oxygen demand and is associated with myocardial ischemia.[18] In a coronary artery with a high grade stenosis, the supply response is limited, and can result in supply-demand mismatch MI when myocardial oxygen demand increases.

Consistent with this hypothesis, two small retrospective autopsy studies (<70 patients in total) reported that two-thirds of the patients who suffered a fatal perioperative MI had significant left main or 3 vessel coronary artery disease.[19 20] Most patients did not exhibit plaque fissuring and only about one-third had an intracoronary thrombus. Although the timing of the autopsies relative to the MIs may have allowed resolution of intracoronary thrombus, these data suggest that some fatal perioperative MIs are secondary to supply-demand mismatch.

1.2.1.2 Potential role of coronary thrombus in the pathophysiology of perioperative MI

An alternative mechanism of perioperative MI is that the acute stress of surgery and mechanical tissue injury induce a hypercoagulable-inflammatory state that increases the risk of coronary thrombus formation. The sympathetic hyperactivity associated with surgery promotes hypercoagulability by up-regulating coagulation and platelets and down-regulating fibrinolysis.[21-23] The increase in perioperative catecholamines is also associated with an increase in coronary shear stress, which may trigger plaque fissuring and acute coronary thrombosis.[24] Noncardiac surgery also results in inflammation (e.g., an increase in tumor necrosis factor α [TNF-α], interleukin [IL] -6, and IL-8) that may have a direct role in initiating plaque fissuring and acute coronary thrombosis.[25]

A small study of 21 patients who suffered a perioperative MI who had undergone a coronary angiography prior to vascular surgery revealed that the majority of nonfatal perioperative MIs occurred in arteries without a high-grade stenosis, suggesting that these events may have resulted from an acute coronary artery thrombosis.[26] Further evidence to support the thrombosis hypothesis comes from the Coronary Artery Revascularization Prophylaxis (CARP) Trial.[27] This trial randomized 510 patients undergoing elective vascular surgery who had at least one coronary artery with a $\geq$ 70% stenosis that was suitable for revascularization to receive coronary artery revascularization or no coronary artery revascularization before vascular surgery. This trial failed to demonstrate a significant reduction in the risk of perioperative MI in the patients randomized to undergo coronary revascularization. If supply-demand mismatch is the cause of perioperative MI, one would expect the risk of perioperative MI to decrease with coronary revascularization prior to noncardiac surgery.

Given the limitations of the evidence, it is not possible to draw firm conclusions regarding the pathophysiology of perioperative MI. It is likely that both mechanisms of perioperative MI (i.e., supply-demand mismatch and coronary thrombus) account for a portion of the perioperative MIs. Figure 1 summarizes the physiological changes that occur with surgery and how they may result in an MI. A perioperative prevention trial would ideally impact both proposed mechanisms to provide the greatest potential for benefit.

1.2.2 Laboratory and physiology evidence suggests clonidine may prevent death and nonfatal MIs in patients undergoing noncardiac surgery

Like beta-blockers, alpha-2 agonists (e.g., clonidine) attenuate the perioperative stress response, but they do so through a different mechanism. Alpha-2 agonists act on central and presynaptic receptors to inhibit the release of norepinephrine leading to a reduction in central sympathetic outflow.[28 29] Clonidine, the most available alpha-2 agonist, has a number of attributes that make it attractive as a potential agent to prevent perioperative MI and death. Perioperative clonidine induces sympatholysis,[30 31] has analgesic[32-34] and anti-shivering effects,[35] reduces myocardial oxygen uptake,[36] and reduces TNF-α, IL-6, and IL-8.[37 38] A meta-analysis of 2 noncardiac surgery clonidine RCTs (total 358 patients)

found a reduction in myocardial ischemia (based upon Holter recordings) with clonidine, without an increased risk of hemodynamic instability.[39] Perioperative clonidine trials have also demonstrated that clonidine decreases the average heart rate during the perioperative period.[30 31 40] Given these physiological changes, which may minimize the risk of supply-demand mismatch (i.e., sympatholytic, analgesic, and anti-shivering effects) and thrombus formation (i.e., sympatholytic, analgesic, and anti-inflammatory effects), clonidine may prevent major perioperative vascular events without incurring an increased risk of events mediated through hemodynamic instability, particularly stroke.

1.2.3 Experimental evidence and relevant systematic reviews evaluating the effects of alpha-2 agonists and clonidine in patients undergoing noncardiac surgery

1.2.3.1 Alpha-2 agonist data

A meta-analysis of alpha-2 agonists (clonidine, dexmedetomidine, mivazerol) included 12 noncardiac surgery RCTs.[41] The authors of this systematic review reported separately the results for patients who had vascular surgery and patients who had nonvascular noncardiac surgery. The meta-analysis demonstrated a statistically significant reduction in both death (39 events; relative risk [RR] 0.47; 95% CI, 0.25-0.90) and MI (110 events; RR 0.66; 95% CI 0.46-0.94) with alpha-2 agonist therapy among the vascular surgery patients. The investigators found no effect on mortality (31 events; RR 1.09; 95% CI 0.52-2.09) and MI (62 events; RR 1.25; 95% CI 0.83-2.21) among the nonvascular noncardiac surgery patients. The 6 trials that reported hypotension did not suggest an increase in hypotension with an alpha-2 agonist (RR 1.03; 95% CI 0.89-1.21).

The likelihood of a true subgroup effect is low.[42] Although there were 12 RCTs included in this meta-analysis, a single trial of mivazerol accounted for 80% of the deaths and 91% of the MIs.[43] While this trial randomized 2854 patients, the published report excludes 957 of these patients at high risk of coronary artery disease in whom an interim analysis demonstrated a lower than expected event rate.[43] The investigators reported on the remaining 1897 patients with established coronary artery disease among whom 91 (9.5%) assigned mivazerol and 100 (10.6%) assigned placebo suffered a death or nonfatal MI (risk ratio 0.89; 95% CI, 0.67-1.18). The authors reported a statistically significant reduction in this composite outcome with mivazerol only for the subgroup of vascular surgery patients, but there was no interaction P value reported and no prior hypothesis for a subgroup effect.

1.2.3.2 POISE-2 Pilot Trial

Since this prior meta-analysis, we have conducted the POISE-2 Pilot. We report here the data on the first 60 patients included in this pilot, Table 1. In the POISE-2 Pilot 6 of 30 clonidine patients versus 10 of 30 placebo patients developed clinically important hypotension. Although the POISE-2 Pilot is small these results are encouraging and suggest that the POISE-2 clonidine regimen may allow us to obtain the benefits we demonstrated in POISE-1 while mitigating the risks that appeared to have primarily occurred through clinically important hypotension.

1.2.3.3 Updated perioperative clonidine meta-analysis

The outdated perioperative clonidine meta-analysis mentioned above (section 1.2.2) included only 2 noncardiac surgery clonidine trials.[39] We therefore conducted a systematic review and meta-analysis of clonidine given to patients undergoing noncardiac surgery, which also includes the POISE-2 Pilot data. Thirty-two RCTs met our eligibility criteria.[30 31 33 36 37 40 44-68]

Table 2 reports the perioperative clonidine meta-analysis results. There was a statistically significant reduction in mortality with clonidine (RR 0.27; 95% CI, 0.07-0.99), but there were only 10 deaths in total making this result unreliable. The MI, stroke, and congestive heart failure results are also encouraging but limited by few events. Myocardial ischemia was less common among the patients randomized to clonidine (19.3%) compared to control (31.0%) (RR 0.66; 95% CI, 0.49-0.89).

Table 3 reports the clinically important hypotension results. The results demonstrate a significant increase in clinically important hypotension with clonidine (RR 1.51; 95% CI, 1.20-1.91), but there was moderate heterogeneity (I^2 31%). Our a priori hypothesis for heterogeneity based upon low-

dose clonidine (daily effective dose < 0.3 mg) versus high-dose clonidine (daily effective dose ≥ 0.3mg) explained this heterogeneity. The trials evaluating high-dose clonidine, but not those evaluating low-dose clonidine, demonstrated a significant increase in clinically important hypotension (P value for the test of interaction between these subgroups was < 0.01). Importantly, the low-dose clonidine trials showed the same positive trends as the high-dose clonidine trials regarding the other outcomes (e.g., mortality). Since clinically important hypotension had the largest population-attributable risk for stroke in POISE-1, the results suggest we will not find an increased risk of stroke with low-dose clonidine.

A meta-analysis of the low-dose clonidine RCTs demonstrates that low-dose clonidine reduces heart rate (mean difference = -5.94; 95% CI, -9.61, -2.27). No trials reported any rebound hypertension after discontinuation of the short courses of perioperative clonidine.

1.2.4 Perioperative clonidine may reduce intermediate-term mortality

An elevated troponin measurement after surgery is an independent predictor of death at 1 year. It has been hypothesized that perioperative ischemia results in unstable coronary plaques that are prone to fissuring weeks to months later, resulting in cardiac events.[69] This hypothesis, if correct, would explain how clonidine (which prevents perioperative myocardial ischemia) might, even after its discontinuation, affect intermediate-term (i.e., 1 year) vascular events.

Wallace and colleagues undertook an RCT evaluating the effect of 4 days of perioperative clonidine in patients undergoing noncardiac surgery.[31] Clonidine demonstrated an absolute risk reduction (ARR) of 5.4% for mortality at 30 days (total of 5 deaths, p=0.048) and demonstrated an ARR of 14% for mortality at 2 years (total of 38 deaths, p=0.035). These encouraging but limited data (Wallace is the only clonidine trial that reported following patients beyond 30 days) highlight the need for further RCTs to examine whether perioperative clonidine reduces intermediate-term mortality.

1.2.5 Current perioperative clonidine practices and feasibility of a perioperative clonidine RCT

We are currently conducting a 40,000 patient prospective cohort study (i.e., VISION) in 10 centres in 7 countries. VISION is evaluating a representative sample of patients ≥ 45 years of age who are undergoing noncardiac surgery. Of the first 6000 patients included in VISION, 2839 fulfilled the POISE-2 eligibility criteria and only 1.2% of these patients received an alpha-2 agonist sometime during the perioperative period. These data demonstrate that clonidine is used infrequently in the perioperative setting; indicating that the available information on clonidine has not impacted clinical practice. These data also indicate that it should not be difficult to recruit patients into a perioperative clonidine trial, as confirmed by our POISE-2 pilot where 3 centres enrolled 60 patients, and each centre recruited on average > 3 patients per week. The infrequent routine use of perioperative clonidine and our rapid recruitment rate in the POISE-2 Pilot demonstrate the feasibility of the POISE-2 Trial.

1.2.6 Observational and experimental evidence regarding the effects of initiating and withdrawing ASA in the <u>non-operative</u> setting

The Antithrombotic Trialists' Collaboration undertook a meta-analysis of RCTs evaluating the effects of initiating anti-platelet therapy. This non-operative meta-analysis included 195 trials involving 135,640 patients and 17,207 major vascular events. This meta-analysis demonstrated that ASA reduced nonfatal MI by one third, nonfatal stroke by one quarter, and mortality by one sixth in patients with or at high risk of atherosclerotic disease.[70] This meta-analysis also demonstrated that low-dose ASA (75-150 mg daily) was as effective but less gastrotoxic than higher doses, but in acute settings an initial loading dose of 160 mg of ASA (which is sufficient to provide rapid and complete inhibition of TXA_2 mediated platelet aggregation)[71] may be required.[72]

A recent meta-analysis of 3 prospective cohort studies that included 34,344 patients evaluated the effects of discontinuing ASA in the non-operative setting.[73] ASA discontinuation was associated with an increased risk for thrombotic events (RR 1.82; 95% CI, 1.52-2.18; $I^2 = 0\%$).

1.2.7 Laboratory and physiology evidence that suggests ASA may prevent vascular death and nonfatal myocardial infarctions in patients undergoing noncardiac surgery

Immediately after noncardiac surgery, patients experience a rise in circulating platelet release products.[74] Platelet surface catalyzing coagulation reactions facilitate thrombin generation and these events may promote thrombus formation and lead to arterial occlusion in the perioperative setting.[25] Acute withdrawal of chronic ASA results in a pro-thrombotic state (i.e., increased thromboxane A_2 [TXA_2] and decreased fibrinolysis).[75 76] Given these physiological changes, ASA initiation or, for chronic users, ASA continuation - and the associated inhibition of platelet aggregation - may prevent major perioperative vascular events through inhibition of thrombus formation.[77]

1.2.8 Experimental evidence and relevant systematic reviews evaluating the effects of ASA in patients undergoing noncardiac surgery

We have undertaken a systematic review and meta-analysis of perioperative ASA trials that included patients undergoing any type of noncardiac surgery. Fifteen RCTs fulfilled eligibility criteria and are included in our systematic review.[78-92]

Table 4 reports our perioperative ASA meta-analysis results. Both all-cause mortality (RR 0.85; 95% CI, 0.63-1.14) and vascular mortality (RR 0.59; 95% CI, 0.28-1.25) show trends towards benefit from perioperative ASA. In contrast, 58 of 9069 patients assigned ASA and 43 of 9037 patients assigned control suffered a nonfatal MI (RR 1.31; 95% CI, 0.88-1.94). This trend towards harm was identified in trials that did not routinely monitor daily cardiac biomarkers after surgery, except for the POISE-2 Pilot, and in total there were only a moderate number of nonfatal MIs. The meta-analysis did not demonstrate an impact on nonfatal stroke with perioperative ASA (total 125 events; RR 0.91; 95% CI 0.64-1.29), and suggested a trend towards fewer nonfatal pulmonary emboli with ASA (total 91 events; RR 0.74; 95% CI, 0.49-1.11). Perioperative ASA demonstrated an increase in major bleeding (total 357 events; RR 1.47; 95% CI, 1.19-1.80).

Although there were 19 trials in our ASA meta-analyses the Pulmonary Embolism Prevention (PEP) Trial dominated contributing the majority of patients and events.[85] PEP was a trial of hip fractures focused on pulmonary emboli, and they did not monitor for perioperative MI with daily troponin measurements. PEP provides important information, but there is a need for a large perioperative ASA trial that includes the majority of noncardiac surgeries and actively monitors for perioperative MIs.

1.2.9 Low versus high-dose ASA

The only surgical trial that has compared low versus high-dose ASA randomized patients undergoing carotid endarterectomy to low-dose ASA (i.e., 709 patients assigned 81 mg/day and 708 patients assigned 325 mg/day) and they had a lower risk (i.e., 6.2%) of the primary outcome (i.e., a composite of death, nonfatal MI, and nonfatal stroke at 3 months) than the patients randomized to high-dose ASA (i.e., 715 patients assigned 650 mg/day and 717 patients assigned 1300 mg/day) of which 8.4% suffered the primary outcome, P 0.03.[93] Recently the CURRENT OASIS-7 Trial was presented at the European Society of Cardiology 2009 Congress. This trial of 2 low-doses of ASA randomized 25,087 patients suffering an acute coronary syndrome to ASA 75-100 mg per day versus ASA 300-325 mg per day. At 30 day follow-up there was no difference between the groups regarding major cardiovascular outcomes (i.e., cardiovascular death, myocardial infarction, and stroke). Given this evidence we will evaluate low-dose ASA 100mg per day in POISE-2.

1.2.10 Current perioperative ASA practices and feasibility of a perioperative ASA trial

In POISE-1, 36.1% of the participants took ASA sometime in the week prior to surgery, and 39.7% took ASA sometime during their hospital admission. Because 84% of the patients in POISE-1 underwent general, orthopedic, or vascular surgery, we conducted a cross-sectional survey of all practicing Canadian general, orthopedic, and vascular surgeons.[94] Our survey demonstrated marked variations among surgeons regarding the starting and holding of ASA around the time of surgery. A majority of respondents also reported a willingness to have their patients participate in a perioperative ASA trial. Our survey identified the need for, and support of, a large randomized trial of perioperative ASA

among patients undergoing noncardiac surgery. Our recruitment rate in the POISE-2 Pilot demonstrates the feasibility of recruiting patients into a perioperative ASA trial.

1.2.11 Summary of why POISE-2 is needed now

Laboratory and physiology evidence suggests clonidine may minimize the risk of supply-demand mismatch and thrombus formation; perioperative trial evidence demonstrates clonidine prevents myocardial ischemia and suggests clonidine may prevent MI and mortality in both the short and intermediate-term. Perioperative trials also suggest low-dose clonidine does not result in hemodynamic instability, making an increase in stroke less likely. Despite this evidence, clonidine is uncommonly used in the perioperative setting. The need for a large adequately powered perioperative low-dose clonidine trial to settle the issue in a clear way that will drive subsequent practice is compelling.

Laboratory and physiological evidence suggests that ASA initiation or, for chronic users, ASA continuation may prevent major perioperative vascular events. The perioperative trial evidence suggests ASA may prevent mortality, but the effect on MI is unclear and the increased risk of bleeding is imprecise. There is overwhelming RCT evidence in the non-operative setting that ASA prevents death, MI, and, stroke. Observational data suggest that ASA discontinuation in the non-operative setting results in adverse thrombotic events. A perioperative carotid endarterectomy RCT of 2849 patients demonstrated improved outcomes with low-dose ASA compared to high-dose ASA. Our national survey demonstrates that perioperative ASA usage is variable, identifying the need for, and community interest in, a large perioperative low-dose ASA trial.

2.0 PLAN OF INVESTIGATION

2.1 Trial Objectives

2.1.1 Primary efficacy objectives

To determine the impact of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.

2.1.2 Secondary efficacy objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 30 days after randomization: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, amputation, peripheral arterial thrombosis, infection/sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization.

3. To determine in each ASA stratum the impact on a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization.

2.1.3 Safety objectives

1. To determine the impact of perioperative low-dose clonidine on each of the following individual outcomes at 30 days after randomization: stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure.

2. To determine the impact of perioperative low-dose ASA on each of the following individual outcomes at 30 days after randomization: stroke, life-threatening bleeding, and major bleeding.

2.1.4 One year follow-up objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on all-cause mortality and nonfatal MI at 1 year after randomization.

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1 year after randomization.

3. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 1 year after randomization: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, amputation, peripheral arterial thrombosis, new diagnosis of cancer, diagnosis of recurrent cancer and rehospitalization for vascular reason.

2.2 Trial Design

POISE-2 is an international RCT of 10,000 patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery. Utilizing a 2X2 factorial design, POISE-2 will determine the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo in the perioperative setting. Patients, health care providers, data collectors, and outcome adjudicators will be blind to treatment allocation.

2.3 Sample Size

Our perioperative meta-analysis suggested that clonidine had an RR of 0.27 for mortality and 0.45 for MI, but the confidence intervals were wide. Given the multitude of pathogenic mechanisms associated with perioperative MI, it is only realistic to expect a moderate relative treatment effect[95] (as was the case in POISE-1).[5] Therefore, we assume clonidine will result in a HR of 0.75 for the primary outcome (all-cause mortality or nonfatal MI). Our perioperative meta-analysis suggested ASA had a RR of 0.85 for all-cause mortality and 1.31 for nonfatal MI, but the confidence intervals were wide. The MI data are inconsistent with the overwhelming evidence in the non-operative setting in which ASA results in a RR of 0.70 for MI.[70] Further, the observational ASA withdrawal data suggest an increased risk of thrombotic events with ASA discontinuation.[73] Therefore, we believe it is more probable that ASA will result in a moderate treatment effect consistent with a HR of 0.75 for the primary outcome.

Table 5 presents our sample size calculations. We used the control event rate for all-cause mortality and nonfatal MI in POISE-1 and adjusted this event rate accounting for the factorial design (i.e., both interventions will have a HR of 0.75), and this suggests a placebo event rate of 6.1%. Our sample size calculation also takes into account patients discontinuing their study drug. We will undertake a trial of at least 10,000 patients as this will provide 84% power if our event rate is 6.1% and 81% power if our event rate is 5.6% (2-sided alpha = 0.05).

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients are eligible if they:

1. are undergoing noncardiac surgery;
2. are ≥ 45 years of age;
3. are expected to require at least an overnight hospital admission after surgery; AND
4. fulfill ≥ 1 of the following 5 criteria:
   - A. history of coronary artery disease as defined by any one of the following 6 criteria
     - i. history of angina
     - ii. history of a myocardial infarction or acute coronary syndrome
     - iii. history of a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging
     - iv. history of a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia
     - v. history of a coronary angiographic or CT coronary angiographic evidence of atherosclerotic stenosis ≥ 50% of the diameter of any coronary artery
     - vi. ECG with pathological Q waves in two contiguous leads

vii. previous coronary artery revascularization, i.e. percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)

B. history of peripheral vascular disease as defined by a physician diagnosis of a current or prior history of any one of the following 4 criteria

i. intermittent claudication
ii. vascular surgery for atherosclerotic disease
iii. an ankle/arm systolic blood pressure ratio $\leq$ 0.90 in either leg at rest
iv. angiographic or doppler study demonstrating $\geq$ 70% stenosis in a noncardiac artery

C. history of stroke as defined by any one of the following 2 criteria

i. a physician diagnosis of stroke
ii. CT or MRI evidence of a prior stroke

D. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, carotid endarterectomies, and endovascular abdominal aortic aneurysm repair (EVAR); OR

E. any 3 of 9 risk criteria

i. undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal or major orthopedic surgery (i.e., hip arthroplasty, internal fixation of hip or femur, pelvic arthroplasty, knee arthroplasty, above-knee amputation or amputation below the knee but above the foot)
ii. history of congestive heart failure defined as a physician diagnosis of a current or prior episode of congestive heart failure OR prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema
iii. history of a transient ischemic attack;
iv. diabetes and currently taking an oral hypoglycemic agent or insulin;
v. age $\geq$ 70 years;
vi. hypertension;
vii. serum creatinine > 175 μmol/L (> 2.0 mg/dl);
viii. history of smoking within 2 years of surgery;
ix. undergoing emergent/urgent surgery defined as surgery that a surgeon schedules to go to the operating room within 48 hours of an acute presentation to the hospital

3.2 Exclusion Criteria

We will exclude patients meeting any of the following criteria:

1. consumption of ASA within 72 hours prior to surgery;
2. hypersensitivity or known allergy to ASA or clonidine;
3. systolic blood pressure < 105 mm Hg;
4. heart rate < 55 beats per minute in a patient who does not have a permanent pacemaker;
5. second or third degree heart block without a permanent pacemaker;
6. active peptic ulcer disease or gastrointestinal bleeding within previous 6 weeks;
7. intracranial hemorrhage (including subdural hematoma and parenchymal hematoma as a complication of primary ischemic stroke) documented by neuro-imaging, in the 6 months prior to randomization. This does not include petechial hemorrhagic transformation of a primary ischemic stroke;
8. subarachnoid hemorrhage or epidural hematoma unless the event occurred more than 6 months prior to randomization and the offending aneurysm or arterial lesion has been repaired;
9. drug-eluting coronary stent in the year prior to randomization;[96]
10. bare-metal coronary stent in the 6 weeks prior to randomization;[96]
11. thienopyridine (e.g., clopidogrel, ticlopidine, prasugrel) or ticagrelor within 72 hours prior to surgery; or intent to restart a thienopyridine or ticagrelor during the first 7 days post-op; or

currently taking an alpha-2 agonist, alpha methyldopa, monoamine oxidase inhibitors or reserpine;

12. planned use – during the first 3 days after surgery – therapeutic dose anticoagulation (e.g., dabigatran > 250 mg/day, or rivaroxaban > 10 mg/day) or a therapeutic subcutaneous or intravenous antithrombotic agent (defined as full dose unfractionated heparin [i.e., > 15, 000 u/24hrs], low molecular weight heparin [i.e., > 6,000 u/24hrs or enoxaparin: > 60 mg/24hrs], or fondaparinux [i.e., > 2.5mg/24hrs];
13. undergoing intracranial surgery, carotid endarterectomy, or retinal surgery;
14. not consenting to participate in POISE-2 prior to surgery; OR
15. previously enrolled in POISE-2 Trial

4.0 PATIENT RECRUITMENT AND INFORMED CONSENT

We will utilize efficient recruitment strategies we developed in POISE-1. In the majority of centres, research personnel will screen the patient list in the preoperative assessment clinic to identify eligible patients. Research personnel will use a variety of screening approaches to capture patients who do not attend the preoperative assessment clinic, including screening: the daily surgical list in the operating room, patients on surgical wards and intensive care units, and patients in the preoperative holding area. Centres will also use all potential patient sources including asking the services of anesthesia, surgery, and medicine to page the study personnel regarding all surgical admissions through the emergency department and consultations for ward patients requiring surgery. Research personnel will approach all eligible patients to obtain informed consent. POISE-2 will enroll patients from approximately 150 centres in 16 countries.

5.0 RANDOMIZATION

Randomization will occur prior to surgery (goal is 2 to 4 hours pre-op) for all eligible patients for whom informed consent is obtained. Research personnel will randomize patients via a 24-hour computerized randomization phone service at the coordinating centre at the Population Health Research Institution (PHRI) at the Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. The randomization process will use block randomization stratified by centre. Study centre personnel will not know the block size. We will randomize patients in a 1:1:1:1 fashion to receive clonidine/ASA, clonidine/ASA placebo, clonidine placebo/ASA, or clonidine placebo/ ASA placebo. Patients in the ASA Continuation Stratum and ASA Starting Stratum will be evenly assigned to each of the 4 randomization groups. Approximately half the POISE-2 patients will come from each ASA stratum (i.e., we will ensure that each ASA stratum constitutes as least 45% of the overall trial population, as we were able to achieve in the POISE-2 Pilot).

6.0 ADMINISTRATION OF STUDY MEDICATION

Medical orders will include all drug administration protocols.

6.1 Clonidine or Placebo

Prior to surgery (goal 2-4 hours) patients fulfilling hemodynamic requirements (i.e., systolic blood pressure $\geq$ 105 mm Hg and a heart rate $\geq$ 55 bpm) will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The clonidine patch releases clonidine at a constant rate (0.2 mg/day) for 7 days. Patients will have the patch removed at 72 hours after surgery. No cases of clonidine withdrawal hypertension have been reported with transdermal clonidine, therefore we do not require a tapering process.[97] If the patient is discharged before 72 hours post-op, then the study coordinator will phone the patient to remind the patient to remove the patch at 72 hours post-op.

Oral clonidine is absorbed rapidly and reaches peak serum concentrations within 2-4 hours and demonstrates physiological effects (e.g., a decrease in heart rate) within 1 hour; these effects persist for 24 hours.[98 99] Transdermal clonidine reaches peak serum concentrations at 48 hours after application, demonstrates physiological effects at 24 hours; after removal of the clonidine patch serum

concentrations and physiological effects can persist for 2 -3 days.[100] Giving oral clonidine 2-4 hours before surgery will allow us to achieve physiological effects before surgery and these effects will persist for 24 hours. Applying the transdermal patch 2-4 hours before surgery will allow us to achieve physiological effects starting around the time the effects of the oral clonidine dose are resolving. This dosing regimen is consistent with a low-dose clonidine regimen (i.e., an effective dose < 0.3 mg/day).

6.2 ASA or Placebo

We will enrol patients in 1 of 2 ASA strata. The ASA Continuation Stratum will involve patients who are taking ASA chronically; we will randomize these patients to continue ASA or withdraw ASA and take a placebo. The ASA Starting Stratum will involve patients who are not taking ASA chronically; we will randomize these patients to start ASA or placebo. All patients will be randomized on the day of surgery, and approximately half the POISE-2 patients will come from each ASA stratum, as supported by our prior research (i.e., POISE-2 Pilot). Patients in both ASA strata will receive the same trial ASA intervention (i.e., either ASA 100 mg or matching placebo). For the first dose prior to surgery (goal 2-4 hours) they will take 2 tablets orally. After the first dose, patients will take 1 tablet daily for 30 days in the Starting Stratum and 7 days in the Continuation Stratum, after which they will resume their regular ASA. Patients who are not able to take ASA orally will receive it rectally.

We will consider patients who have taken ASA daily for at least 1 month within a 6 week period prior to surgery to be on ASA chronically, and we will enrol these patients in the ASA Continuation Stratum. In this stratum, we will include patients who have had their ASA withheld sometime in the 2 weeks before surgery. No ASA is allowed for 72 hours prior to surgery (outside of the study drug), and if a patient has taken ASA in the 72 hours before surgery they are ineligible.

Our decision to allow patients to participate in the Continuation Stratum even if they have taken their ASA 73 hours prior to surgery was based upon the following 2 points. First, the mean life span of human platelets is approximately 8 to 10 days, and about 12% of circulating platelets are replaced every 24 hours.[101 102] In patients treated with ASA it may take 10 days for the total platelet population to be renewed, and thus restore normal COX-1 activity. O'Brien has demonstrated, however, that abnormal platelet aggregation after ingestion of aspirin can be corrected ex vivo by 10% normal platelet rich plasma.[102] Further, it has been reported that if as little as 20% of platelets have normal COX-1 activity, hemostasis is normal.[103 104] Therefore stopping ASA for 72 hours is likely to ensure substantial (if not complete) recovery of platelet function. Second, in the ISIS-2 Trial that randomized 17,187 patients to ASA or placebo in the acute MI setting, they included patients who were taking ASA chronically even if they took ASA on the day of their MI.[72] There were 2266 patients in this subgroup, and it demonstrated a statistically significant reduction in vascular death, consistent with the overall finding.[72]

7.0 PLAN TO MINIMIZE RISKS AND MONITORING FOR AND APPROACH TO POTENTIAL PROBLEMS

Perioperative ASA may increase the risk of major bleeding. To minimize this risk, we are excluding patients with active peptic ulcer disease and patients undergoing intracranial or retinal surgery. Further, we are using low-dose ASA in POISE-2.

Multivariable analyses suggested that clinically important hypotension primarily caused the negative outcomes of death and stroke in POISE-1. Perioperative clonidine may result in clinically important hypotension, but we have incorporated many design features into POISE-2 to minimize this risk. In POISE-2 we require patients to have a SBP $\geq$ 105 mm Hg and a heart rate $\geq$ 55 beats per minute (bpm) to be eligible for the trial and to receive the clonidine study drug, whereas in POISE-1 patients received the study drug if they had a SBP $\geq$ 100 mm Hg and their heart rate was $\geq$ 50 bpm. We have also mandated more frequent monitoring of blood pressure and heart rate in POISE-2 (i.e., prior to study drug administration, 1 hour after administration, and Q 4 hours for the first 96 hours after surgery) compared to POISE-1 (i.e., we only required monitoring prior to and during administration of metoprolol). In POISE-2 we are using low-dose clonidine (i.e., < 0.3 mg/day) starting 2-4 hours prior to

surgery and continuing for 72 hours after surgery. The POISE-2 Pilot and our systematic review provide encouraging evidence that low-dose clonidine does not induce clinically important hypotension.

Because non-study antihypertensive medications can also exacerbate the risk of clinically important hypotension we encourage the following approach for all POISE-2 patients:

1. Study personnel will tell POISE-2 patients who are taking an angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), or renin inhibitor to not take any of these medications on the day of surgery. We have conducted a meta-analysis of the 3 RCTs that have randomized patients to either hold or continue their ACE-I or ARB on the day of surgery, Table 6.[105-107] Patients taking their ACE-I or ARB on the day of surgery demonstrated a higher risk of hypotension (RR 7.7; 95% CI, 3.4-17.2, I^2 0%).
2. Study personnel will tell POISE-2 patients who are taking any other anti-hypertensive medications to not take these medications on the morning of surgery but to take these medications to the preoperative surgical holding area.
3. In the preoperative surgical holding area (goal 2-4 hours prior to surgery) study personnel will check the patient's vital signs. Study personnel will convey the patient's hemodynamics to the anesthesiologist or surgeon managing the case and ask if they want the patient to receive any of their non-ACE-I/ARB anti-hypertensive medications and if yes at what dose.

Decisions regarding holding or discontinuing either study drug rest with the attending physician. If a patient develops clinically important hypotension or bradycardia, study personnel will encourage the attending physician to consider fluid resuscitation, administering an inotrope or vasopressor, withholding the patient's non-study antihypertensive medication(s), or if applicable changing the patient's epidural infusion rate. If the patient's clinically important hypotension or bradycardia persists despite these measures or if the patient requires ongoing inotrope or vasopressor administration, study personnel will encourage removal of the patient's clonidine patch. If a patient without a pacemaker develops asystole or a second or third degree heart block that does not quickly resolve and for which there is not a likely alternative explanation (e.g., metabolic abnormality) then study personnel will recommend that removal of the patient's clonidine patch.

If a patient experiences a life-threatening or major bleed, study personnel will recommend that the patient have their ASA trial medication held until the bleeding is stabilized. After the bleeding episode has resolved study personnel will ask the attending physician if they feel it is safe to restart the ASA trial medication.

8.0 OTHER MANAGEMENT AT THE DISCRETION OF THE ATTENDING PHYSICIAN

All aspects of the patient's management are at the discretion of the attending physician. This includes all decisions on antiplatelet, anticoagulation, and anti-ischemic therapies. We will encourage physicians not to prescribe an alpha-2 agonist during the first 4 days after surgery while the clonidine trial medication is likely having an effect (i.e., the first 3 days during administration of the clonidine patch and the 24 hours after removal of the patch when physiological effects are likely to persist). We will also encourage physicians not to prescribe antiplatelet therapy during the initial 7 days after surgery to patients in the ASA Continuation Stratum and for the initial 30 days after surgery to patients in the ASA Starting Stratum (i.e., periods when the patients will receive the ASA trial medication). If specific indications for an alpha-2 agonist or antiplatelet drug arise, the relevant trial medication can be stopped while an open label alpha-2 agonist or ASA is administered. Study personnel will document any open label usage of an alpha-2 agonist or ASA during the first 30 days after surgery.

9.0 FOLLOW-UP

Patient's will have a troponin (or CK-MB if troponin is not available) drawn 6 to 12 hours after surgery and on the first, second, and third days after surgery. Standard orders will dictate these tests are drawn. Standard orders will also ensure patients have an electrocardiogram (ECG) immediately after an elevated troponin is detected. Study personnel will recommend and attempt to obtain an

echocardiogram on patients with an elevated troponin but no ECG changes, ischemic symptoms, or pulmonary edema.

Research personnel will follow patients throughout their time in hospital evaluating the patients and reviewing their medical records ensuring trial orders are followed and noting any outcomes. The research personnel will contact patients by phone at 30 days and 1 year after randomization. If patients indicate that they have experienced an outcome, study personnel will obtain the appropriate documentation.

10.0 TRIAL OUTCOMES

The overall primary outcome of the POISE-2 Trial is a composite of all-cause mortality and nonfatal MI at 30 days after randomization. A secondary outcome includes the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization. Individual secondary outcomes at 30 days after randomization include: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, amputation, peripheral arterial thrombosis, infection/sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis. In each ASA stratum, we will also assess a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization. The safety outcomes in the ASA trial are stroke, congestive heart failure, life-threatening bleeding, and major bleeding at 30 days after randomization. The safety outcomes in the clonidine trial are stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure at 30 days after randomization.

For the 1-year follow-up our primary outcome is all-cause mortality and nonfatal MI. A secondary outcome includes the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1-year after randomization. Secondary 1-year follow-up outcomes include each of the following individual outcomes: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, amputation, peripheral arterial thrombosis, new diagnosis of cancer, diagnosis of recurrent cancer and rehospitalization for vascular reason. Appendix provides definitions for all outcomes.

11.0 ADJUDICATION OF TRIAL OUTCOMES

Outcome adjudicators (a committee of clinicians with expertise in perioperative outcomes) who are blinded to treatment allocation will adjudicate the following outcomes: death (vascular versus non-vascular), MI, nonfatal cardiac arrest, pulmonary emboli, deep venous thrombosis, stroke, life-threatening bleeding, major bleeding, and peripheral arterial thrombosis. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Drs. Gordon Guyatt and Fernando Botto will Co-chair the Adjudication Committee.

12.0 DATA ANALYSES

We will analyze patients in the treatment group to which they are allocated, according to the intention-to-treat principle. We will compare patients allocated to clonidine with patients allocated to clonidine placebo, and we will compare patients allocated to ASA with patients allocated to ASA placebo.

12.1 Main Analyses

We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will use log-rank tests to compare the rate of occurrence of the primary outcome between the ASA versus ASA placebo group and separately the clonidine versus the clonidine placebo group. We will use Cox proportional hazards models to estimate the effect of clonidine, and of ASA, on the hazard ratio for the primary and secondary outcomes (with stratification according to whether treatment included the other agent). We will calculate the hazard

ratios and their associated 95% confidence intervals. We will infer statistical significance if the computed 2-sided p-value is < 0.05. We anticipate that the treatment effect of clonidine and ASA, if present, will act independently, but we will, however, evaluate the possibility of synergism or antagonism by formally testing the interaction term in a Cox model.

12.2 Subgroup Analyses

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the clonidine subgroup analyses (i.e. neuro-axial blockade, vascular surgery, and baseline risk according to number of eligibility criteria) and the ASA subgroup analyses (i.e. ASA stratum, diabetes, creatinine > 175 μmol/L, and baseline risk according to number of eligibility criteria). We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $P < 0.05$.

12.3 Interim Analyses

Three interim efficacy analyses based on the primary outcome will occur when 25%, 50% and 75% of the 30-day data are available. The External Safety and Efficacy and Monitoring Committee (ESEMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) ($\alpha = 0.0001$) for analyses in the first half of the trial and 3 SDs ($\alpha = 0.00047$) for all analyses in the second half.[108 109] For a finding of 1 or both active treatments to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 3 or more months apart. The α-level for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation with subsequent analyses.

The ESEMC will monitor for an adverse impact of clonidine on stroke or mortality, or ASA on stroke, life-threatening bleeding, or mortality. For these analyses, a 3 SDs excess in the first half and a 2.6 SDs excess in the second half of the trial would trigger discussions about stopping for harm.

At any time during the trial if safety concerns arise the ESEMC chairperson will assemble a formal meeting of the full committee. The ESEMC will make their recommendations to the Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered the ESEMC will invite the Operations Committee to explore all possibilities before a decision is made.

13.0 REPORTING SERIOUS ADVERSE EVENTS

We define serious adverse events (SAEs) as those which are fatal, life threatening or fulfill a definition of being clinically important. Efficacy or safety outcomes will not be considered as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition. All events considered as part of the primary, secondary, or safety events (as outlined in section 10.0), should be reported on the appropriate page(s) in the case report forms (CRFs) but not as an SAE, unless considered exceptional in this medical condition.

In this trial, the following events (all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, congestive heart failure, stroke, amputation, peripheral arterial thrombosis, rehospitalization for vascular reasons, life-threatening bleeding, major bleeding, clinically important hypotension, and clinically important bradycardia) are considered related to the underlying cardiovascular disease and are not considered an SAE. These events will not be considered unexpected unless their course, severity or other specific features are such that the investigator, according to his/her best medical judgment, considers these events as exceptional in the context of the patient's medical condition.

Only unexpected and not previously described serious adverse events that are believed with a reasonable level of certainty to be associated with the trial medication need to be reported immediately (i.e. within 24 hours of knowledge of the event) to the Central Coordinating Office. For such events research personnel should complete an SAE CRF and immediately enter it into the iDatafax Database

System or fax it to the Project Office, who will then inform the sponsor and the regulatory bodies.

14.0 TRIAL MANAGEMENT

14.1 What are the Arrangements for the Day to Day Management of the Trial?

Figure 2 illustrates the organizational structure of POISE-2 and Table 7 describes the trial timetable. The Population Health Research Institute (PHRI) Project Office, McMaster University, Hamilton, Canada is the coordinating center for this trial and is primarily responsible for the development of the trial protocol, organization of the trial, development of the randomization scheme, the trial database, data internal consistency checks, data analyses, and coordination of the trial centres. The POISE-2 Principal Investigator, Project Officer, Project Manager, and Coordinator are responsible for the activities of the Project Office. Dr. P.J. Devereaux is the Principal Investigator (PI), and he is responsible for the overall supervision of the trial. Dr. Devereaux was the Co-PI of the largest perioperative cardiac RCT (POISE-1), and he is the PI of the largest international perioperative vascular complications prospective cohort study (VISION). Dr. Marko Mrkobrada is the Project Officer, and he is responsible for providing clinical support to the trial and providing guidance to the Trial Coordinator.

The Project Manager (Ms. Susan Chrolavicius) has extensive experience running large cardiovascular trials, and she will oversee the Trial Coordinator (Ms. Andrea Robinson) who has experience in large international trials. The POISE-2 Trial Coordinator is responsible for the daily conduct of the trial including supervising the data management assistant (who is responsible for data validation and quality); supplying centres with POISE-2 posters, pocket cards, and a detailed Manual of Operations that will outline each step of the protocol; producing and presenting to the Principal Investigator, Project Officer, and Project Manager: monthly reports on screening, patient follow-up, data transmission, consistency and thoroughness of data collection, and event rates; transmitting these reports to sites; develop and transmit to all trial investigators and research personnel weekly enrolment reports; monitoring and contacting any centres with high rates of eligible but not enrolled patients to discuss procedures and establish solutions to problems; communication with investigators and research personnel regarding protocol and other procedural questions; answer the project office's toll free phone number that investigators and trial personnel can call to resolve any problems or questions that arise; coordination of supplying study drug and aids; writing and distributing quarterly trial newsletters; maintenance of required documentation for regulatory agencies; review of all events prior to adjudication, compilation of all the records required for the adjudication process, coordination of the adjudication process, maintenance of the adjudication database; preparation of presentations to the trial committees; organization of Investigator Meetings, Project Office Operations Committee meetings, International Operations Committee meetings, Steering Committee meetings, Adjudication Committee meetings, External Safety and Efficacy and Monitoring Committee, Sub-study and Publications Committee meetings, and weekly project office meetings with the Principal Investigator and Project Officer.

14.2 Project Office Operations Committee and International Operations Committee

The project office is responsible for the day-to-day trial management and will report directly to the Project Office Operations Committee. This committee will consist of P.J. Devereaux, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Salim Yusuf, Gordon Guyatt, Janice Pogue, Dan Sessler, Fernando Botto, Giovanna Lurati, and Andrea Kurz. The Project Office Operations Committee will meet monthly to review trial progress and all pertinent issues related to the conduct of POISE-2. The Project Office Operations Committee will report directly to the International Operations Committee. This committee will include broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the International Operations Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Fernando Botto, Giovanna Lurati, Andrea Kurz, Ganesan Karthikeyan, Pablo Alonso-Coello, Colin Baigent, Otavio Berwanger, Bruce Biccard, Matthew Chan,

Clara Chow, Christian Gluud, Michael Jacka, Giovanni Landoni, Kate Leslie, German Malaga, Martin O'Donnell, Prem Pais, Dan Sessler, Juan Carlos Villar, Chew Wang, and Denis Xavier. The International Operations Committee will hold confererence calls biannually and will review the progress of the trial, international POISE-2 issues, and strategies to ensure the successful conduct and completion of POISE-2.

14.3 The Steering Committee and National Principal Investigators

The International Operations Committee will report to the Steering Committee. We will hold an on-site meeting of the Steering Committee twice during the trial and annual conference calls. At these meetings the International Operations Committee will report to the Steering Committee regarding the overall progress of the trial and plans to ensure successful conduct and completion of POISE-2. For each participating country in POISE-2, the Project Office Operations Committee will appoint a member of the Steering Committee to act as the National Principal Investigator. At the Steering Committee Meetings each National Principal Investigator will provide a brief report to the Steering Committee regarding the country's progress in POISE-2, goals for the coming year, and any issues that require input. The Steering Committee will include a broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the Steering Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Fernando Botto, Giovanna Lurati, Andrea Kurz, Ganesan Karthikeyan, Pascal Alfonsi, Pablo Alonso-Coello, Sonia Anand, Andrew Auerbach, Colin Baigent, Packianathaswamy Balaji, Scott Beattie, Otavio Berwanger, Mohit Bhandari, Bruce Biccard, Norm Buckley, Matthew Chan, Clara Chow, David Conen, Deborah Cook, Jim Douketis, John Eikelboom, Patrice Forget, Amit Garg, Hertzel Gerstein, Bill Ghali, Christian Gluud, Michelle Graham, Robert Hart, Michael Hill, Andreas Hoeft, Michael Jacka, Eric Jacobsohn, Clive Kearon, Andre Lamy, Giovanni Landoni, Kate Leslie, German Malaga, Finlay McAlister, Danny McAuley, Christian Meyhoff, Scott Miller, Peter Nagele, Martin O'Donnell, Prem Pais, Joel Parlow, Dan Sessler, Thomas Schricker, Marko Simunovic, Sadeesh Srinathan, Kevin Teoh, David Torres Perez, Gerard Urrutia, Juan Carlos Villar, Michael Walsh, Chew Wang, Richard Whitlock, Duminda Wijeysundera, Denis Xavier, and Homer Yang.

14.4 Centre Principal Investigators

All participating centres will have a Centre Principal Investigator, and this individual is responsible for: (1) obtaining ethics approval from the institutional review board or the ethics board and forwarding this to the Project Office; (2) ensuring study approval is obtained before recruitment starts; (3) ensuring the protocol is followed; (4) ensuring all physicians and nurses involved in the perioperative care of patients undergoing non-cardiac surgery are aware and informed about the POISE-2 Trial (this will involve organizing and presenting educational in-services about the trial and distributing posters and pocket protocols); (5) ensuring that all surgical patients are screened for the trial; (6) ensuring that all enrolled patients have their troponins obtained and ECGs and echocardiograms when appropriate; (7) ensuring that all enrolled patients are followed appropriately; (8) ensuring that all Case Report Forms (CRFs) are promptly and accurately completed and submitted to the Project Office, and that all inquiries from the Project Office regarding patient forms or other matters are addressed promptly; (9) ensuring that a simple screening log is kept of all eligible noncardiac surgery patients who are not enrolled in the POISE-2 Trial and the primary reason they were not enrolled; (10) ensuring they maintain for at least 10 years after the publication of the main results, the list of patient identification numbers and patient names to enable identification of hospital records at a later date.

14.5 Sub-study and Publication Committee

The Project Office Operations Committee will appoint members to a Sub-study and Publication Committee. This committee will create guidelines for sub-studies and publications related to POISE-2. We will publish the main POISE-2 manuscript under group authorship, with the roles of all investigators

acknowledged in an appendix. Subsequent publications will be authored by specific individuals on behalf of the POISE-2 Investigators. Individuals selected to lead the writing of these subsequent publications will depend on their role in and contribution to POISE-2, scientific interest, and scientific expertise.

15.0 OTHER CONSIDERATIONS

15.1 Ensuring Data Quality

Several procedures will ensure data quality including: 1) all research personnel will undergo a training session prior to trial commencement to ensure consistency in trial procedures including data collection and reporting; 2) all centres will have a detailed trial Manual of Operations that will outline each step of the protocol; 3) investigators can use a toll free phone number to a help line at the project office to resolve any problems or questions that arise; 4) the project office personnel will evaluate all data as soon as it is received and quality control checks will identify any errors or omissions; then the project office personnel will notify the sender of any such issues via secure internet, email, telephone, or visit if necessary; 5) the project office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, consistency, thoroughness, and completeness of data collection (e.g., troponin measurements), and event rates, and they will immediately address any identified issues; and 6) the programmer will create internal validity and range checks using the Clinical iDataFax Database System which will identify any errors or omissions and notify the sender and data management assistants of any such issues; 7) the data management assistants will undertake multi-level data validation of the trial Case Report Forms; 8) the Trial Coordinator will (A) send investigators regular quality control reports; (B) obtain from the trial statistician and present to the principal investigator bi-monthly reports on internal validity and range checks using the iDataFax Database System; 9) the study statistician will undertake statistical monitoring every 6 months to identify outliers through (A) comparing centre and data collector variables (e.g., rates of reported primary outcomes), and (B) multivariate tests to examine associations of patient variables across hospitals and data collectors, and 10) we will undertake on-site monitoring at sites based upon the number of patients recruited and for any sites that stand out on statistical monitoring and an experienced monitor will audit a random selection of trial patients with and without a submitted primary outcome case report form.

15.2 Confidentiality and Blinding

All patient information will be stored on a high security computer system and kept strictly confidential. Only the ESEMC and the study statistician who reports to the ESEMC will be aware of the unblinded data until the trial is completed or a recommendation is made to terminate the trial.

15.3 Unblinding

Legitimate situations such as a large overdose of the study drug may require unblinding. We will avoid unblinding when appropriate through use of the following strategy. Prior to unblinding the attending physician will have to complete a detailed checklist to document the reason for unblinding and whether alternatives have been explored. Frequently stopping the study medication, skipping a dose, or giving open label medication will be adequate for the management of most situations. We recommend that all unblinding decisions be made jointly with the Project Office. If after these steps the local study investigator believes emergency unblinding is essential for the patient's management then it can be undertaken.

15.4 Patients Stopping Their Study Medication(s)

Patients can choose to stop their study medication(s) at any time during the course of the trial. Study Personnel will follow patients who make this decision in the same way that they follow all other trial participants. If a patient stops their study medication(s), the Centre Principal Investigator will discuss this decision with the patient. If after this discussion the trial participant decides they want to resume the trial medication(s) the Centre Principal Investigator will re-initiate the study medication(s) if they feel the study medication(s) can be safely restarted.

16.0 POTENTIAL SIGNIFICANCE OF POISE-2

Over 200 million adults annually undergo major noncardiac surgery and 3-5 million will suffer a major vascular complication. POISE-2 will answer two crucial management questions and influence future perioperative practices around the world.

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TABLE 1: POISE-2 Pilot results*

Outcome	Clonidine (N=30)	Clonidine Placebo (N=30)	ASA (N=30)	ASA Placebo (N=30)
Death	0	0	0	0
MI	0	2	1	1
Stroke	1	0	1	0
Cardiac arrest	0	1	1	0
Clinically significant hypotension	6	10	9	7
Clinically significant bradycardia	4	2	6	2
Bleeding	8	10	9	9
CHF	0	1	1	0

* Data from the first 60 patients included in the pilot; CHF = congestive heart failure

TABLE 2: Meta-analysis of trials evaluating perioperative clonidine

Outcome	Trial	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	Wallace[31]	1/125	4/65	0.13	0.01 to 1.14	
	Quintin[33]	0/11	1/10	0.31	0.01 to 6.74	
	Stuhmeier[55]	1/145	2/152	0.52	0.05 to 5.72	
	Total	**2/311**	**8/258**	**0.27**	**0.07 to 0.99**	**0%**
Myocardial infarction						
	Ellis[30]	0/30	2/31	0.21	0.01 to 4.13	
	Wallace[31]	5/125	3/65	0.87	0.21 to 3.51	
	Stuhmeier[55]	0/145	4/152	0.12	0.01 to 2.14	
	POISE-2 Pilot*	0/30	2/30	0.20	0.01 to 4.00	
	Total	**5/330**	**11/278**	**0.45**	**0.15 to 1.33**	**0%**
Nonfatal cardiac arrest						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	

	Total	**0/60**	**2/61**	**0.34**	**0.04 to 3.17**	**0%**
Stroke					
	Wallace[31]	1/125	0/65	1.57	0.06 to 38.04	
	Schneemilch[57]	0/40	5/40	0.09	0.01 to 1.59	
	POISE-2 Pilot*	1/30	0/30	3.00	0.13 to 70.83	
	Total	**2/195**	**5/135**	**0.69**	**0.07 to 6.37**	**37%**
Congestive heart failure					
	Ellis[30]	4/30	5/31	0.83	0.25 to 2.79	
	Wallace[31]	0/125	2/65	0.10	0.01 to 2.15	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	
	Total	**4/185**	**8/126**	**0.58**	**0.20 to 1.67**	**0%**
Myocardial ischemia					
	Ellis[30]	7/30	8/31	0.90	0.37 to 2.18	
	Wallace[31]	18/125	20/65	0.47	0.27 to 0.82	
	Morris[46]	4/21	4/18	0.86	0.25 to 2.95	
	Pawlik[54]	0/15	1/15	0.33	0.01 to 7.58	
	Stuhmeier[55]	35/145	59/152	0.62	0.44 to 0.88	
	Lipszyc[58]	8/20	5/20	1.60	0.63 to 4.05	

Matot[59]	0/18	2/18	0.20	0.01 to 3.89	
Total	**72/374**	**99/319**	**0.66**	**0.49 to 0.89**	**8%**

* = POISE-2 Pilot results after recruitment of 60 patients

TABLE 3: Meta-analysis of perioperative clonidine trials, clinically important hypotension results

Outcome and Subgroup	Trial	Outcome definition	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Clinically important hypotension							
Low-dose clonidine (< 0.3mg/day)							
	Nader[37]	MAP 20% lower than baseline BP	2/7	2/8	1.14	0.21 to 6.11	
	Lemes[44]	MAP < 60 mmHg or 30% lower than baseline BP	1/33	0/35	3.18	0.13 to 75.33	
	Mayson[45]	SBP 25% lower than baseline BP	18/24	13/19	1.10	0.75 to 1.61	
	Morris[46]	MAP 20% lower than baseline BP	5/21	3/18	1.43	0.40 to 5.17	
	Sia[47]	SBP 20% lower than baseline BP	4/50	3/50	1.33	0.31 to 5.65	
	Stapelfeldt[48]	SBP < 90 mmHg	15/17	12/17	1.25	0.88 to 1.78	
	Stuhmeier[55]	MAP < 70 mmHg	20/145	26/152	0.81	0.47-1.38	
	Schneemilch[57]	MAP 20% lower than basline BP and treated with cafedrine/theoadrenaline	19/40	5/40	3.80	1.57 to 9.18	
	Fehr[60]	MAP < 50mmHg or >20% drop from pre-induction value	10/25	10/25	1.00	0.51 to 1.97	
	Rhee[61]	MAP 30% lower than baseline BP	5/52	1/26	2.50	0.31 to 20.31	

	Vanderstappen[62]	MAP 20% lower than preinduction value treated with ephedrine	4/140	2/140	2.00	0.37-10.74	
	Watanabe[63]	SBP < 90mmHg	8/22	4/20	1.82	0.65-5.12	
	POISE-2 Pilot*	SBP < 90 mm Hg that required an intra-aortic balloon pump, inotropic agent, fluid resuscitation, or study drug discontinuation	6/30	10/30	0.60	0.25 to 1.44	
	Subtotal		**117/606**	**91/580**	**1.19**	**0.95 to 1.49**	**12%**
High-dose clonidine (≥ 0.3mg/day)							
	Ellis[30]	SBP < 90 mmHg, unresponsive to fluid challenge	2/30	3/31	0.69	0.12 to 3.84	
	Wallace[31]	SBP < 80mmHg lasting ≥ 5 minutes	24/125	11/65	1.13	0.59-2.17	
	Quintin[33]	DBP < 90mmHg lasting more than 3 minutes intraoperatively or more than 5 minutes postoperatively	5/11	2/10	2.27	0.56 to 9.20	
	Pluskwa[40]	SBP < 100 mmHg lasting more than 3 minutes	12/14	8/15	1.61	0.96 to 2.70	
	Owen[49]	MAP 20% lower than baseline BP	14/15	4/14	3.27	1.41 to 7.56	
	Park[50]	SBP < 90 mmHg	8/22	2/22	4.00	0.95 to 16.75	
	Parlow[51]	SBP < 90 mmHg	2/10	0/10	5.00	0.27 to 92.62	
	Takahasi[52]	SBP < 80mmHg	17/21	5/17	2.75	1.28 to 5.92	

	Matot[59]	Intraprocedural drop in SBP more than 30% from preinduction value or absolute SBP < 90mmHg	2/18	0/18	5.00	0.26 to 97.37
	Bernard[64]	MAP < 60mmHg	2/16	0/16	5.00	0.26 to 96.59
	Bernard[65]	MAP ≤ 60mmHg	3/25	0/25	7.00	0.38 to 128.87
	Sarkar[66]	SBP < 80mmHg and treated with ephedrine	2/22	1/21	1.91	0.19 to 19.52
	Wright[67]	SBP < 80mmHg	14/30	0/30	29.00	1.81-465.07
	Subtotal		**107/359**	**36/294**	**2.13**	**1.47 to 3.09** **18%**
All trials (i.e., both low and high-dose)						
	Total		**231/1031**	**132/941**	**1.51**	**1.20 to 1.91** **31%**

OR = odds ratio; SBP = systolic blood pressure; MAP = mean arterial blood pressure; BP = blood pressure; DBP = diastolic blood pressure; * = POISE-2 Pilot results after recruitment of 60 patients

TABLE 4: Meta-analysis of perioperative ASA trials

Outcome	Trial	ASA group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Wood[78]	2/9	2/9	1.00	0.18 to 5.63	
	Goldman[79]	0/22	2/31	0.28	0.01 to 5.53	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	4/32	11/34	0.39	0.14 to 1.09	
	McCollum[82]	40/286	46/263	0.80	0.54 to 1.18	
	Lindblad[83]	1/117	5/115	0.20	0.02 to 1.66	
	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	456/8726	472/8718	0.97	0.85 to 1.09	
	Total	**508/9251**	**538/9229**	**0.85**	**0.63 to 1.14**	**24%**
Vascular mortality						
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	1/32	10/34	0.11	0.01 to 0.78	
	McCollum[82]	15/286	31/263	0.44	0.25 to 0.81	
	Lindblad[83]	0/117	5/115	0.09	0.00 to 1.60	

	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	243/8726	263/8718	0.92	0.78 to 1.10	
	Total	**264/9229**	**310/9198**	**0.59**	**0.28 to 1.25**	**61%**
Nonfatal myocardial infarction						
	McCollum[82]	14/286	14/263	0.92	0.45 to 1.89	
	Nielsen[84]	0/26	1/27	0.35	0.01 to 8.12	
	PEP Trial[85]	43/8726	27/8718	1.59	0.98 to 2.57	
	POISE-2 Pilot	1/31	1/29	0.94	0.06 to 14.27	
	Total	**58/9069**	**43/9037**	**1.31**	**0.88 to 1.94**	**0%**
Nonfatal stroke						
	Findlay[86]	0/10	2/12	0.24	0.01 to 4.42	
	Kretschmer[81]	1/32	2/34	0.53	0.05 to 5.58	
	McCollum[82]	13/286	17/263	0.70	0.35 to 1.42	
	Lindblad[83]	5/117	7/115	0.70	0.23 to 2.15	
	PEP Trial[85]	37/8726	34/8718	1.09	0.68 to 1.73	
	Tytgat[87]	3/50	3/50	1.00	0.21 to 4.72	
	POISE-2 Pilot	1/31	0/29	2.81	0.12 to 66.40	
	Total	**60/9252**	**65/9221**	**0.91**	**0.64 to 1.29**	**0%**

Nonfatal pulmonary embolism					
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24	
	Renney[88]	1/85	1/75	0.88	0.06 to 13.86	
	Harris[89]	0/44	1/51	0.39	0.02 to 9.22	
	McKenna[90]	1/9	3/12	0.44	0.05 to 3.60	
	Alfaro[91]	0/30	1/30	0.33	0.01 to 7.87	
	PEP Trial[85]	36/8726	46/8718	0.78	0.51 to 1.21	
	Total	**38/8903**	**53/8895**	**0.74**	**0.49 to 1.11**	**0%**
Major bleeding					
	McKenna[90]	1/9	0/12	3.90	0.18 to 85.93	
	Green[92]	1/75	0/88	3.51	0.15 to 84.98	
	McCollum[82]	18/286	9/263	1.84	0.84 to 4.02	
	Lindblad[83]	2/117	1/115	1.97	0.18 to 21.38	
	Nielsen[84]	1/26	2/27	0.52	0.05 to 5.39	
	PEP Trial[85]	182/8726	122/8718	1.49	1.19 to 1.87	
	POISE-2 pilot	9/31	9/29	0.94	0.43 to 2.03	
	Total	**214/9270**	**143/9252**	**1.47**	**1.19 to 1.80**	**0%**

TABLE 5: Sample size calculations

Primary Outcome (all-cause mortality or nonfatal MI at 30 days)			**Power (2-sided $\alpha = 0.05$)**		
Control event rate	**% of patients not receiving or prematurely discontinuing study drug ***	**Hazard Ratio**	**N = 9000**	**N=10,000**	**N=11,000**
5.6%	10%	0.75	76.9%	81.1%	84.6%
6.1%	10%	0.75	80.3%	84.3%	87.5%

* Based on POISE-2 Pilot among patients discontinuing clonidine prematurely the discontinuation rate was 80% on the first day and 20% on the second day.

TABLE 6: Meta-analysis of trials evaluating preoperative management of ACE-I and ARB medications

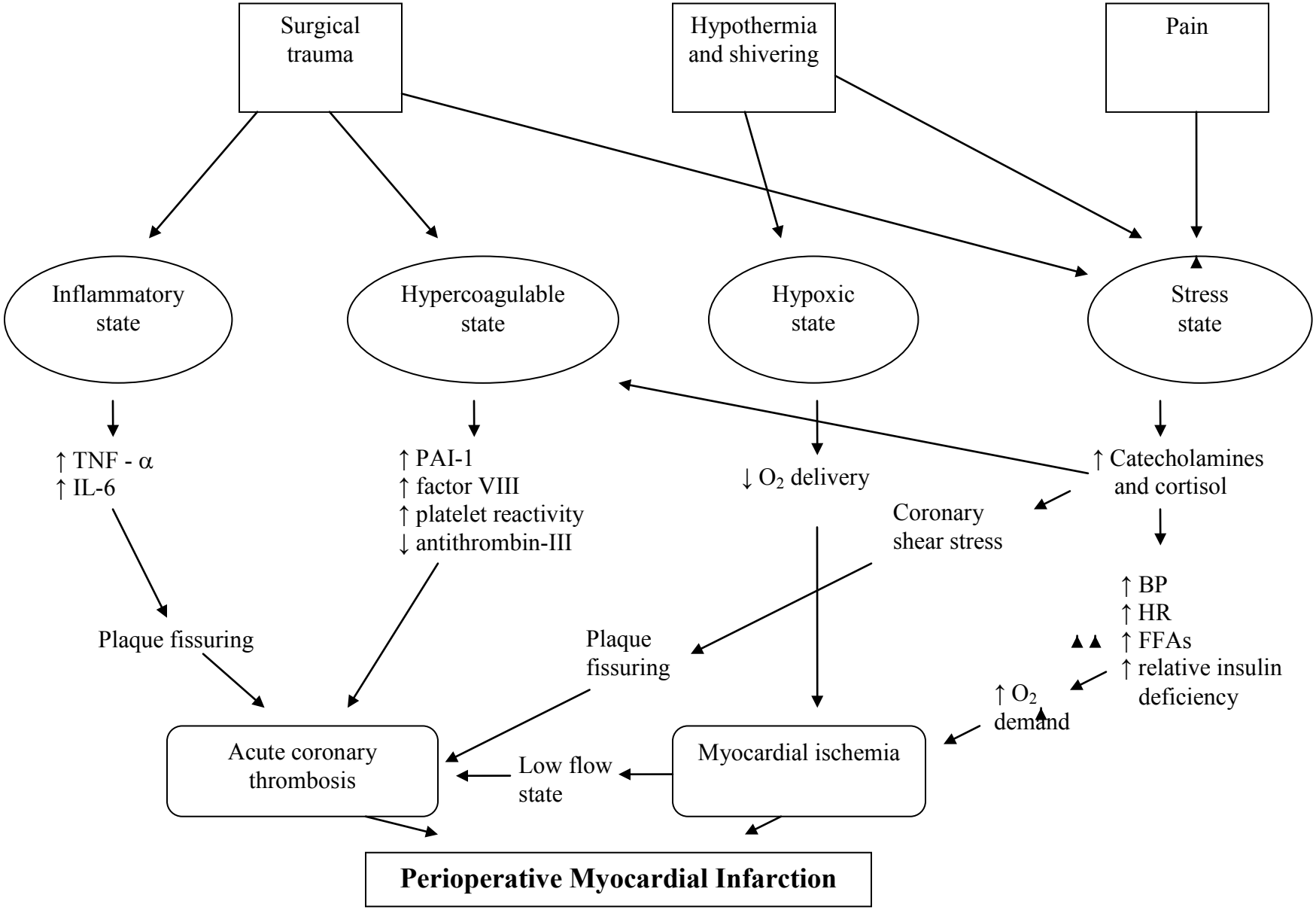
Hypotension						
Trial	**Trial Definition of Intraoperative Hypotension**	**ACE-I/ARB in Immediate Preoperative Period n/N**	**Control group n/N**	**Relative risk**	**95% CI**	**I^2**
Schirmer[105]	Mean arterial blood pressure <60 mmHg	17/50	5/50	4.6	1.6 to 13.8	
Bertrand[106]	Systolic blood pressure <80 mmHg longer then 1 minute	19/19	12/18	20.3	1.05 to 392.5	
Coriat[107]	Systolic blood pressure <90 mmHg	16/21	6/30	12.8	3.34 to 49.1	
Total		**52/90**	**23/98**	**7.7**	**3.4 to 17.2**	**0%**

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

TABLE 7: POISE-2 trial timeline

Phase	Time (months)	Tasks
1 (planning)	6	1. Meeting of investigators for discussion of protocol and finalization of procedures 2. Translation of the protocol into non-English languages 3. Development of all study aids 4. Study approval by local ethics committee 5. Health Canada Approval and regulatory approval in other countries 6. Drug packaging and kit preparation, 7. Development of randomization sequence 8. Shipping trial materials 9. Ensure local teams are ready to start recruitment to avoid delays during recruitment phase
2 (recruitment)	36	Recruitment of 10,000 patients
3 (short-term follow-up)	1	All patients are actively followed for 1 month including all patients enrolled at the end of the recruitment phase
4 (completion of short-term study)	6	1. Data clean-up 2. Confirmation and classification of events 3. Data analysis 4. Publication of primary and secondary results
5 (long-term follow-up)	5	All patients are actively followed for 1 year.
6 (completion of long-term study)	6	1. Data analysis 2. Publication of primary and secondary results

FIGURE 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

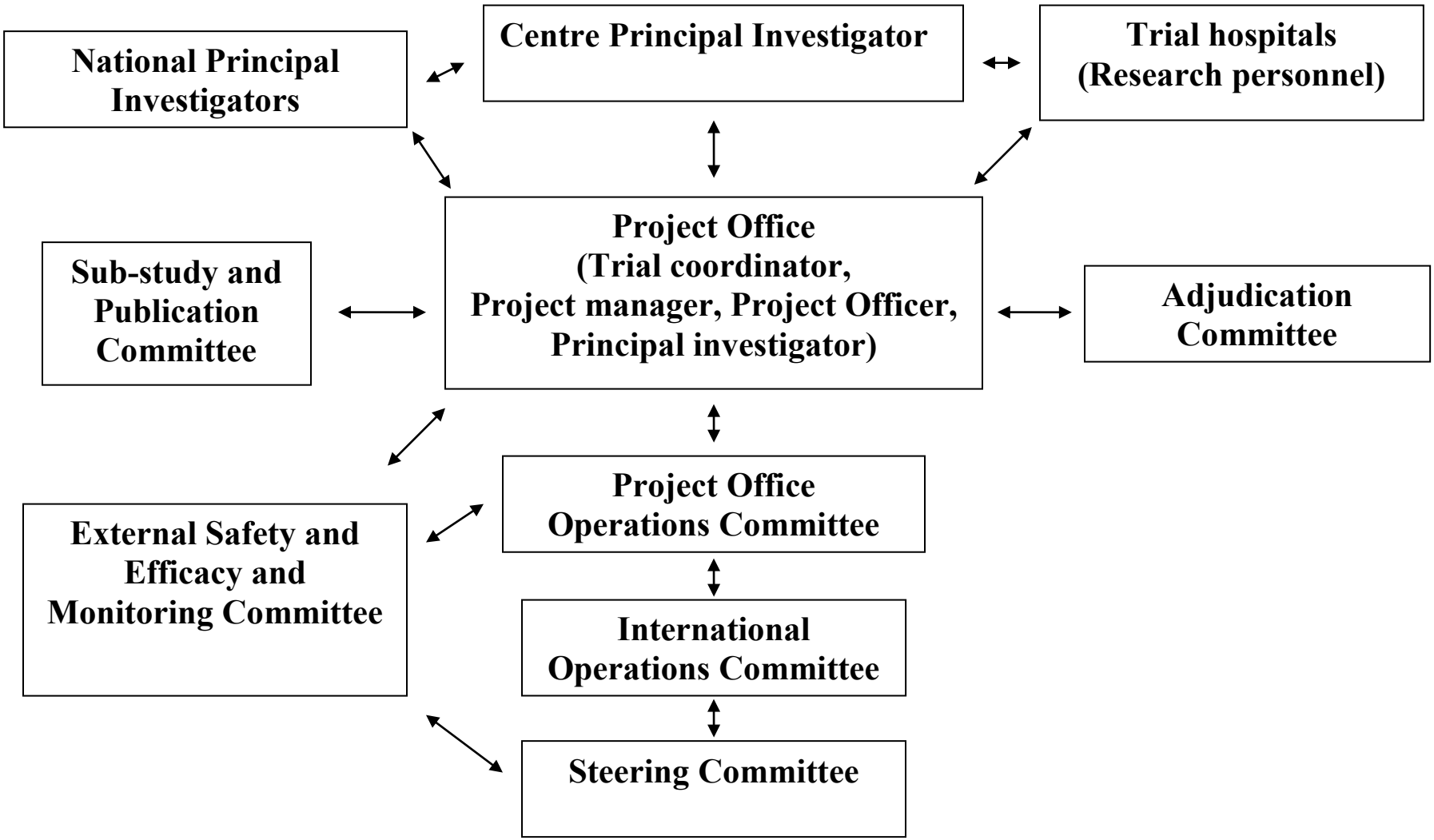


LEGEND

Figure 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

TNF-α = tumor necrosis factor α, IL-1 = interleukin-1, IL-6 = interleukin-6, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor -1, O_2 = oxygen, BP = blood pressure, HR = heart rate, FFAs = free fatty acids

FIGURE 2: POISE-2 Organizational Structure



APPENDIX: POISE-2 outcome definitions

1. Sub-classification of death

Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).

2.0 Myocardial infarction

The diagnosis of MI requires any one of the following criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also requires that 1 of the following must also exist:
   - A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)
   - B. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds
   - C. ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads
   - D. coronary artery intervention (i.e., PCI or CABG surgery)
   - E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
2. Pathologic findings of an acute or healing myocardial infarction
3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

3. Nonfatal cardiac arrest

Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

4. Cardiac Revascularization Procedures

Cardiac revascularization procedures include PCI and CABG surgery.

5. Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.

6. Pulmonary embolus (PE)

The diagnosis of PE requires any one of the following:

1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
   - A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan
   - B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

7. Deep venous thrombosis (DVT) of leg or arm

The diagnosis of DVT requires any one of the following:

1. A persistent intraluminal filling defect on contrast venography
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography

3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

8. New Clinically Important Atrial Fibrillation

New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

9. Re-hospitalization for Vascular Reasons

Re-hospitalization for vascular reasons is defined as re-hospitalization for MI, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolus, any vascular surgery, or bleeding.

10. Life-threatening bleeding

Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

11. Major bleeding

Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" above, and results in a postoperative hemoglobin ≤ 70 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in a hemoglobin drop of ≥ 50 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in the patient receiving a transfusion of ≥ 4 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); OR is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

12. Clinically important hypotension

Clinically important hypotension is defined as a systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.

13. Clinically important bradycardia

Clinically important bradycardia is defined as a heart rate < 55 beats per minute requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.

15. Congestive heart failure

The definition of congestive heart failure requires at least one of the following clinical signs (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) **and** at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

16. New acute renal failure requiring dialysis

Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

17. Amputation

Amputation is defined as an amputation procedure subsequent to the initial surgery.

18. Peripheral Arterial Thrombosis

We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis:

1) Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism
2) Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism
3) Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism
4) Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism

19. Infection/Sepsis

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or

body cavity by pathogenic or potentially pathogenic organisms. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38^{o}C or < 36^{o}C; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^{9}/L or < 4 x 10^{9}L.

20. New diagnosis of cancer since surgery. Defined as a patient with a new diagnosis of cancer (i.e., the patient has no prior history of this cancer) within the first 12 months after their initial surgery for which they were enrolled in POISE-2. This outcome is for all cancers except non-melanoma skin cancers.

21. Diagnosis of recurrent cancer since surgery. Defined as patients with **any diagnosis of recurrent cancer** (i.e., a recurrence of a previous cancer for which the patient received curative treatment) within the 12 months after their initial surgery for which they were enrolled in POISE-2. Recurrent cancer does not include non-melanoma skin cancers.

POISE-2 protocol changes

Below we outline the location and change to the protocol highlighted in bold.

We have changed the ASA dose from 81 mg day to 100mg per day as this is the dose that Bayer International will provide.

Page 10 second last paragraph section 1.2.9: Given this evidence we will evaluate low-dose ASA **100mg** per day in POISE-2.

Based on the CIHR reviews we have excluded patients with a recent GI bleed, recent intracranial or subarachnoid hemorrhage or epidural hematoma, those taking ticagrelor and prasugrel, and those with planned use of therapeutic dose anticoagulation during the first 3 days after surgery.

Page 13 section 3.2 exclusion criteria:
6. active peptic ulcer disease **or gastrointestinal bleeding within previous 6 weeks;**
7. intracranial hemorrhage (including subdural hematoma and parenchymal hematoma as a complication of primary ischemic stroke) documented by neuro-imaging, in the 6 months prior to randomization. This does not include petechial hemorrhagic transformation of a primary ischemic stroke;
8. subarachnoid hemorrhage or epidural hematoma unless the event occurred more than 6 months prior to randomization and the offending aneurysm or arterial lesion has been repaired;

11. currently taking an alpha-2 agonist, alpha methyldopa, reserpine, **ticagrelor, or thienopyridine** (e.g., clopidogrel, ticlopidine, **prasugrel**);
12. planned use – during the first 3 days after surgery – therapeutic dose anticoagulation (e.g., warfarin with a target INR $\geq$ 2.0, dabigatran > 250 mg/day, or rivaroxaban > 10 mg/day) or a therapeutic subcutaneous or intravenous antithrombotic agent (defined as full dose unfractionated heparin [i.e., > 15, 000 u/24hrs], low molecular weight heparin [i.e., > 6,000 u/24hrs or enoxaparin: > 60 mg/24hrs], or fondaparinux [i.e., > 2.5mg/24hrs];

Page 14 last paragraph section 6.2: Patients in both ASA strata will receive the same trial ASA intervention (i.e., either ASA **100 mg** or matching placebo).

Based on the CIHR reviews we will increase the vital sign monitoring for the first 96 hours post surgery.

Page 15 4th paragraph section 7.0: We have also mandated more frequent monitoring of blood pressure and heart rate in POISE-2 (i.e., prior to study drug administration, 1 hour after administration, **and Q 4 hours for the first 96 hours after surgery)** compared to POISE-1 (i.e., we only required monitoring prior to and during administration of metoprolol).

Based on the CIHR reviews we make it clear that we are not recommending to continue study clonidine drug if a patient requires ongoing inotrope or vasopressor support.

Page 16 2nd paragraph: If the patient's clinically important hypotension or bradycardia persists despite these measures o**r if the patient requires ongoing inotrope or vasopressor administration,** study personnel will encourage removal of the patient's clonidine patch.

Based on the CIHR reviews we will add a subgroup analysis based on baseline risk.

Page 17 section 12.2: Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the clonidine subgroup analyses (i.e. neuro-axial blockade, vascular surgery, **and baseline risk according to number of eligibility criteria**) and the ASA subgroup analyses (i.e. ASA stratum, diabetes, creatinine > 175 μmol/L, **and baseline risk according to number of eligibility criteria**).

We are very happy to report that Dan Sessler has taken a part time appointment at McMaster and with his time at McMaster he will now join the Project Office Operation Committee.

Page 19 second paragraph section 14.2: This committee will consist of P.J. Devereaux, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Salim Yusuf, Gordon Guyatt, Janice Pogue, **Dan Sessler,** and Kristian Thorlund.

We are also very happy to report that Dr. David Conen will join the Steering Committee as the National PI for Switzerland.

Page 19 last paragraph section 14.3: At the initiation of the POISE-2 Trial the Steering Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Kristian Thorlund, Ganesan Karthikeyan, Pablo Alonso-Coello, Sonia Anand, Andrew Auerbach, Colin Baigent, Scott Beattie, Otavio Berwanger, Mohit Bhandari, Bruce Biccard, Norm Buckley, Matthew Chan, Clara Chow, **David Conen,** Deborah Cook, Jim Douketis, John Eikelboom, Jim Eisenach, Amit Garg, Bill Ghali, Christian Gluud, Michelle Graham, Robert Hart, Claes Held, Michael Hill, Michael Jacka, Eric Jacobsohn, Clive Kearon, Andre Lamy, Giovanni Landoni, Kate Leslie, German Malaga, Finlay McAlister, Paul Myles, Peter Nagele, Martin O'Donnell, Prem Pais, Joel Parlow, Dan Sessler, Thomas Schricker, Marko Simunovic, Sadeesh Srinathan, Wojciech Szczeklik, Kevin Teoh, David Torres Perez, Gerard Urrutia, Juan Carlos Villar, Michael Walsh, Chew Wang, Jørn Wetterslev, Richard Whitlock, Duminda Wijeysundera, Denis Xavier, and Homer Yang.

POISE-2 protocol changes (version date: March 1, 2010)

Below we outline the location and change to the protocol highlighted in bold.

To comply with the CIHR reviews we have added one 30 day and 1 year composite outcome on page 11 and 12.

2.1.2 Secondary efficacy objectives

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization.

2.1.4 One year follow-up objectives

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1 year after randomization.

We have also added these outcomes on pages 16 and 17.

10.0 TRIAL OUTCOMES

The overall primary outcome of the POISE-2 Trial is a composite of all-cause mortality and nonfatal MI at 30 days after randomization. **A secondary outcome includes the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization.** Individual secondary outcomes at 30 days after randomization include: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis. In each ASA stratum, we will also assess a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization. The safety outcomes in the ASA trial are stroke, congestive heart failure, life-threatening bleeding, and major bleeding at 30 days after randomization. The safety outcomes in the clonidine trial are stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure at 30 days after randomization.

For the 1-year follow-up our primary outcome is all-cause mortality and nonfatal MI. **A secondary outcome includes the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1-year after randomization.** Secondary 1-year follow-up outcomes include each of the following individual outcomes: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, and rehospitalization for vascular reason. Appendix provides definitions for all outcomes.

POISE-2 protocol changes (version date: April 6, 2011)

The following minor protocol amendments were made based on the experience gained during the first 8 months of conducting the POISE-2 Trial. The modifications are intended to reduce risks and to expand the secondary outcomes evaluated by this trial. Bold font indicates the changes.

Title page:
In order to specify that Population Health Research Institute is the sponsor of POISE-2 and indicate that this document is confidential, we have updated the title page:

- **Sponsor and Coordinating Centre:**
- This protocol has been developed by the POISE-2 Steering Committee and its contents are the **confidential** intellectual property of this group.

Page 3 Summary:
Since it is a major surgery, retroperitoneal surgery was added as a type of major surgery that is considered a risk factor. Therefore, the summary on Page 3 was updated:

- Inclusion Criteria E. "any 3 of the following 9 criteria: undergoing major surgery (i.e. intraperitoneal, intrathoracic, **retroperitoneal,** or major orthopedic surgery)…"

2.1.2 Secondary efficacy objectives, Item 1:
Amputation, peripheral arterial thrombosis and infection/sepsis are newly added secondary outcome events at 30 days. Therefore, 2.1.2 Secondary efficacy objectives, Item 1 was updated:
1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 30 days after randomization: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, **amputation, peripheral arterial thrombosis, infection/sepsis,** rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

2.1.4 One year follow-up objectives, Item 3:
Amputation, peripheral arterial thrombosis, new diagnosis of cancer and diagnosis of recurrent cancer are newly added secondary outcome events at 1 year. Therefore, 2.1.4 One year follow-up objectives, Item 3 was updated:
3. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 1 year after randomization: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, **amputation, peripheral arterial thrombosis, new diagnosis of cancer, diagnosis of recurrent cancer** and rehospitalization for vascular reason.

3.1 Inclusion Criteria, Item A:
Previous coronary artery revascularization is evidence of a prior history of coronary artery disease and therefore was added to this definition. Therefore, 3.1 Inclusion Criteria, Item A was updated:
A. history of coronary artery disease as defined by any one of the following 6 criteria
i. history of angina
ii. history of a myocardial infarction or acute coronary syndrome
iii. history of a segmental cardiac wall motion abnormality on echocardiography
or a segmental fixed defect on radionuclide imaging

iv. history of a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia
v. history of a coronary angiographic or CT coronary angiographic evidence of atherosclerotic stenosis ≥ 50% of the diameter of any coronary artery
vi. ECG with pathological Q waves in two contiguous leads
vii. previous coronary artery revascularization, i.e. percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)

3.1 Inclusion Criteria, Item D:
We do not consider endovascular abdominal aortic aneurysm repair as a major vascular surgery and therefore it was removed from the definition of major vascular surgery. Patients undergoing EVAR are still potentially eligible but they have to fulfill another eligibility criteria. Therefore, 3.1 Inclusion Criteria, Item D was updated:
D. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, carotid endarterectomies, **and endovascular abdominal aortic aneurysm repair (EVAR);** OR

3.1 Inclusion Criteria, Item E (i):
Since it is a major surgery, retroperitoneal surgery was added as a type of major surgery that is considered a risk factor. Therefore, 3.1 Inclusion Criteria, Item E (i) was updated:
i. undergoing major surgery defined as intraperitoneal, intrathoracic, **retroperitoneal** or major orthopedic surgery

3.2 Exclusion Criteria:
To reduce the risk of perioperative bleeding, the use of antiplatelet medications such as thienopyridine and ticagrelor in the 72 hours prior to surgery or intent to use them during the first 7 days post-op is now excluded. As well, the current use of monoamine oxidase inhibitors is also excluded for the same reason. Therefore, 3.2 Exclusion Criteria was updated:
11. **thienopyridine (e.g., clopidogrel, ticlopidine, prasugrel) or ticagrelor within 72 hours prior to surgery; or intent to restart a thienopyridine or ticagrelor during the first 7 days post-op; or** currently taking an alpha-2 agonist, alpha methyldopa, **monoamine oxidase inhibitors** or reserpine;

3.2 Exclusion Criteria:
Achieving full dose anticoagulation with warfarin during the first 3 days post-op is not feasible. Achieving full dose anticoagulation during the first 3 days after surgery is uncommon and usually restricted to patients with mechanical heart valves receiving bridging therapy. This will almost always occur with full dose IV heparin or full dose low molecular weight heparin. Therefore, warfarin was removed from this exclusion criteria because it is not realistic that a patient will go to surgery with a therapeutic INR and continue warfarin immediately after surgery and maintain their INR in the therapeutic range during the first 3 days after surgery. Therefore, 3.2 Exclusion Criteria was updated:
12. planned use – during the first 3 days after surgery – therapeutic dose anticoagulation (e.g., ~~**warfarin with a target INR ≥ 2.0,**~~ dabigatran > 250 mg/day, or rivaroxaban > 10 mg/day) or a therapeutic subcutaneous or intravenous antithrombotic agent (defined as full dose unfractionated heparin [i.e., > 15, 000 u/24hrs], low molecular weight heparin [i.e., > 6,000 u/24hrs or enoxaparin: > 60 mg/24hrs], or fondaparinux [i.e., > 2.5mg/24hrs];

5.0 Randomization, First Paragraph, First Sentence:
Coordinating the randomization and pre-op study drug administration in early morning surgical cases can be difficult due to time constraints. While it is optimal to randomize the patient 2 to 4 hours pre-op, this timeframe is a goal and not mandatory. Therefore this sentence was modified to make this clear. Patients can be randomized as long as they can get the study drug prior to surgery (i.e., anytime prior to surgery). Therefore, 5.0 Randomization, First Paragraph, First Sentence was updated:
Randomization will occur prior to surgery **(goal is 2 to 4 hours pre-op)** for all eligible patients for whom informed consent is obtained.

6.1 Clonidine or Placebo, First Paragraph, Last Sentence:
A phone call to the patient ensures that the patch is not left on for longer than required by protocol. Therefore, 6.1 Clonidine or Placebo, First Paragraph, Last Sentence has been updated to include:
If the patient is discharged before 72 hours post-op, then the study coordinator will phone the patient to remind the patient to remove the patch at 72 hours post-op.

7.0 Plan to minimize risks and monitoring for and approach to potential problems, Item 1:
Renin inhibitors can also exacerbate the risk of clinically important hypotension, and therefore to reduce the risk of this occurring in trial subjects, we encourage study personnel to ask trial subjects not to take renin inhibitors on the day of surgery. Therefore, 7.0 Plan to minimize risks and monitoring for and approach to potential problems, Item 1 was updated:

1. Study personnel will tell POISE-2 patients who are taking an angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), **or renin inhibitor** to not take any of these medications on the day of surgery.

10.0 Trial Outcomes, First Paragraph, Third Sentence:
Amputation, peripheral arterial thrombosis and infection/sepsis are newly added secondary outcome events at 30 days. Therefore, 10.0 Trial Outcomes, First Paragraph, Third Sentence was updated:
Individual secondary outcomes at 30 days after randomization include: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, **amputation, peripheral arterial thrombosis, infection/sepsis,** rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

10.0 Trial Outcomes, Second Paragraph, Third Sentence:
Amputation, peripheral arterial thrombosis, new diagnosis of cancer and diagnosis of recurrent cancer are newly added secondary outcome events at 1 year. Therefore, 10.0 Trial Outcomes, Second Paragraph, Third Sentence was updated:
Secondary 1-year follow-up outcomes include each of the following individual outcomes: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, **amputation, peripheral arterial thrombosis, new diagnosis of cancer and diagnosis of recurrent cancer** and rehospitalization for vascular reason.

11.0 Adjudication of Trial Outcomes:
Peripheral arterial thrombosis is a newly added secondary outcome and will be adjudicated. Also, in order for the adjudication committee to operate efficiently, Fernando Botto will replace Ganesan

Karthikeyan as co-chair of the adjudication committee, because Dr. Botto is available in Hamilton, Canada for regular meetings. Therefore, 11.0 Adjudication of Trial Outcomes was updated:
Outcome adjudicators (a committee of clinicians with expertise in perioperative outcomes) who are blinded to treatment allocation will adjudicate the following outcomes: death (vascular versus non-vascular), MI, nonfatal cardiac arrest, pulmonary emboli, deep venous thrombosis, stroke, life-threatening bleeding, major bleeding, and **peripheral arterial thrombosis**. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Drs. Gordon Guyatt and **Fernando Botto** will Co-chair the Adjudication Committee.

12.3 Interim Analyses, First Paragraph, Third Sentence:
For a finding ~~**in favor**~~ of 1 or both active treatments to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 3 or more months apart.

13.0 Reporting Serious Adverse Events, Second Paragraph, First Sentence:
Since amputation and peripheral arterial thrombosis are considered related to the underlying cardiovascular disease, these events will not be considered as Serious Adverse Events. Therefore, 13.0 Reporting Serious Adverse Events, Second Paragraph, First Sentence has been updated:
In this trial, the following events (all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, congestive heart failure, stroke, **amputation, peripheral arterial thrombosis,** rehospitalization for vascular reasons, life-threatening bleeding, major bleeding, clinically important hypotension, and clinically important bradycardia) are considered related to the underlying cardiovascular disease and are not considered an SAE.

14.2 Project Office Operations Committee and International Operations Committee, First Paragraph, Second Sentence:
The project office is responsible for the day-to-day trial management and will report directly to the Project Office Operations Committee. This committee will consist of P.J. Devereaux, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Salim Yusuf, Gordon Guyatt, Janice Pogue, Dan Sessler, ~~**Kristian Thorlund,**~~ **Fernando Botto, Giovanna Lurati, and Andrea Kurz.**

14.2 Project Office Operations Committee and International Operations Committee, First Paragraph, Sixth Sentence:
At the initiation of the POISE-2 Trial the International Operations Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, ~~**Kristian Thorlund,**~~ **Fernando Botto, Giovanna Lurati, Andrea Kurz,** Ganesan Karthikeyan, Pablo Alonso-Coello, Colin Baigent, Otavio Berwanger, Bruce Biccard, Matthew Chan, Clara Chow, Christian Gluud, ~~**Claes Held,**~~ Michael Jacka, Giovanni Landoni, Kate Leslie, German Malaga, ~~**Paul Myles,**~~ Martin O'Donnell, Prem Pais, Dan Sessler, ~~**Wojciech Szczeklik,**~~Juan Carlos Villar, Chew Wang, ~~**Jorn Wettersley**~~, and Denis Xavier.

14.3 The Steering Committee and National Principal Investigators, First Paragraph, Seventh Sentence:
At the initiation of the POISE-2 Trial the Steering Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, ~~**Kristian Thorlund,**~~ **Fernando Botto, Giovanna Lurati, Andrea Kurz,** Ganesan Karthikeyan, **Pascal Alfonsi,** Pablo Alonso-Coello, Sonia Anand, Andrew Auerbach, Colin Baigent, **Packianathaswamy Balaji,** Scott Beattie, Otavio Berwanger, Mohit Bhandari, Bruce Biccard, Norm

Buckley, Matthew Chan, Clara Chow, David Conen, Deborah Cook, Jim Douketis, John Eikelboom, ~~**Jim Eisenach,**~~ **Patrice Forget,** Amit Garg, **Hertzel Gerstein,** Bill Ghali, Christian Gluud, Michelle Graham, Robert Hart, ~~**Claes Held,**~~ Michael Hill, **Andreas Hoeft,** Michael Jacka, Eric Jacobsohn, Clive Kearon, Andre Lamy, Giovanni Landoni, Kate Leslie, German Malaga, Finlay McAlister, ~~**Paul Myles,**~~ **Danny McAuley, Christian Meyhoff, Scott Miller,** Peter Nagele, Martin O'Donnell, Prem Pais, Joel Parlow, Dan Sessler, Thomas Schricker, Marko Simunovic, Sadeesh Srinathan, ~~**Wojciech Szczeklik,**~~ Kevin Teoh, David Torres Perez, Gerard Urrutia, Juan Carlos Villar, Michael Walsh, Chew Wang, ~~**Jørn Wetterslev,**~~ Richard Whitlock, Duminda Wijeysundera, Denis Xavier, and Homer Yang.

Appendix: POISE-2 outcome definitions - Item 17, 18, 19, 20 and 21:

In order to specify the definition for the newly added secondary outcomes, Appendix: POISE-2 outcome definitions, Item 17, 18, 19, 20 and 21 have been added:

17. Amputation

Amputation is defined as an amputation procedure subsequent to the initial surgery.

18. Peripheral Arterial Thrombosis

We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis:

1) **Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism**
2) **Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism**
3) **Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism**
4) **Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism**

19. Infection/Sepsis

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38^{o}C or < 36^{o}C; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^{9}/L or < 4 x 10^{9}L.

20. New diagnosis of cancer since surgery. Defined as a patient with a new diagnosis of cancer (i.e., the patient has no prior history of this cancer) within the first 12 months after their initial surgery for which they were enrolled in POISE-2. This outcome is for all cancers except non-melanoma skin cancers.

21. Diagnosis of recurrent cancer since surgery. Defined as patients with any diagnosis of recurrent cancer (i.e., a recurrence of a previous cancer for which the patient received curative treatment) within the 12 months after their initial surgery for which they were enrolled in POISE-2. Recurrent cancer does not include non-melanoma skin cancers.

PeriOperative ISchemic Evaluation-2 (POISE-2) Trial

SHORT-TERM STATISTICAL ANALYSIS PLAN

POPULATION HEALTH RESEARCH INSTITUTE

12:30 PM, January 3, 2014

1. TRIAL OBJECTIVES

Primary Efficacy Objective:

1. To determine the impact of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of mortality or nonfatal myocardial infarction (MI) in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.

Secondary Efficacy Objectives:

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of mortality, nonfatal MI, and nonfatal stroke up to 30 days after randomization.

2. To determine among all the ASA patients the impact on a composite outcome of mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis up to 30 days after randomization and whether the effects differ from each other in each ASA stratum.

Tertiary Efficacy Objectives:

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes up to 30 days after randomization: mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, amputation, peripheral arterial thrombosis,

infection, sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

Safety Objectives:

1. To determine the impact of perioperative low-dose clonidine on each of the following individual outcomes up to 30 days after randomization: stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure.
2. To determine the impact of perioperative low-dose ASA on each of the following individual outcomes up to 30 days after randomization: stroke, clinically important hypotension, congestive heart failure, life-threatening bleeding, and major bleeding.

2. TRIAL OUTCOME EVENTS

Primary Efficacy Outcome for Clonidine and ASA

1. The primary efficacy outcome is the first occurrence of any component of the following composite up to day 30 after randomization: mortality or nonfatal myocardial infarction (MI).

Secondary Efficacy Outcomes

1. A secondary efficacy outcome for clonidine and ASA is the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, or nonfatal stroke.

2. A secondary efficacy outcome among all the ASA patients and whether the effects differ in each of the two ASA strata on the outcome of the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis.

Tertiary Efficacy Outcomes up to 30 Days after Randomization for Clonidine and ASA

1. Mortality
2. Vascular mortality
3. MI
4. Nonfatal cardiac arrest
5. Cardiac revascularization procedure
6. Pulmonary emboli
7. Deep venous thrombosis
8. Clinically important atrial fibrillation
9. Amputation
10. Peripheral arterial thrombosis
11. Infection
12. Sepsis
13. Rehospitalization for vascular reasons
14. Length of hospital stay
15. Length of intensive care unit / cardiac care unit (ICU/CCU) stay

16. New acute renal failure requiring dialysis

Safety Outcomes up to 30 Days after Randomization for Clonidine

1. Stroke
2. Clinically significant hypotension
3. Clinically significant bradycardia
4. Congestive heart failure

Safety Outcomes up to 30 Days after Randomization for ASA

1. Stroke
2. Clinically significant hypotension
3. Congestive heart failure
4. Life-threatening bleeding
5. Major bleeding

The definition of all the outcomes is defined in the Appendix.

3. STATISTICAL AND ANALYTICAL METHODS

Analysis population

All efficacy and safety analyses will include all randomized patients. We will analyze patients in the treatment group to which they were originally allocated. There is no intention to define a per protocol population. We will include all events that centres have reported and the adjudication committee has not refuted.

Efficacy analysis

Primary efficacy analyses

The primary efficacy variable is the first occurrence of mortality or nonfatal myocardial infarction up to 30 days after randomization. We will compare patients allocated to clonidine with patients allocated to clonidine placebo, and we will compare patients allocated to ASA with patients allocated to ASA placebo. Patients lost to follow-up before day 30 after randomization with no primary outcome event reported will be censored at the last day the patient had a complete evaluation of the primary efficacy variable.

The primary efficacy variable will be analyzed using a stratified (i.e., by centre) Cox proportional hazards model. We will address the clonidine objective of superiority through the following hypotheses:

H_0: Hazard ratio of clonidine versus placebo (at 30 days after randomization) = 1

H_a: Hazard ratio of clonidine versus placebo (at 30 days after randomization) ≠ 1

We will consider clonidine superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

We will address the ASA objective of superiority through the following hypotheses:

H_0: Hazard ratio of ASA versus placebo (at 30 days after randomization) = 1

H_a: Hazard ratio of ASA versus placebo (at 30 days after randomization) ≠ 1

We will consider ASA superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

Estimates of the hazard ratios and two-sided 95% confidence intervals will be calculated using the Cox proportional hazards model. If the validity of the proportional hazards assumption is not acceptable, we will compare the proportion of patients with a primary outcome at 30 days after randomization between the two treatment groups, controlling for stratification by centre.

We will also summarize the primary outcome event with Kaplan-Meier curves by treatment group. We will use log-rank tests to compare the rate of occurrence of the primary outcome between the ASA versus the ASA placebo group and separately the clonidine versus the clonidine placebo group.

Primary subgroup analyses on the primary efficacy parameter

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following clonidine subgroup analyses: 1.neuraxial blockade versus no neuraxial blockade (i.e., we expect clonidine to have a greater beneficial effect in patients who did not receive neuraxial blockade compared to patients who did receive neuraxial blockade); 2. vascular surgery versus no vascular surgery (i.e., we expect clonidine to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); and 3. baseline risk according to number of eligibility criteria (i.e., we expect clonidine to have a greater beneficial effect in patients with more eligibility criteria compared to patients with less eligibility criteria).

For the subgroup analyses based on the number of eligibility criteria, we will examine if treatment effect varies across the number of eligibility criteria between the two treatment groups. The eligibility criteria consist of the following variables.

1. history of coronary artery disease
2. history of peripheral arterial disease
3. history of stroke
4. undergoing major vascular surgery
5. any 3 of 9 risk criteria (age ≥70 years; undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery; history of congestive heart failure; history of transient ischemic attack; diabetes and currently taking an oral hypoglycemic agent or insulin; history of hypertension; preoperative serum creatinine >175 μmol/L [>2.0 mg/dl]; smoking within 2 years of surgery; or undergoing emergent/urgent surgery)

The analysis will consist, for each number of eligibility criteria (i.e., 1, 2, 3, 4, or 5), of a stratified Cox proportional hazards model, incorporating terms for treatment group, the individual number of eligibility criteria, and the treatment group by subgroup interaction.

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following ASA subgroup analyses: 1. ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum); 2. baseline risk according to number of eligibility criteria (i.e., we expect ASA to have a greater beneficial effect in patients with more eligibility criteria compared to

patients with less eligibility criteria). The subgroup analyses based on the number of eligibility criteria for ASA will follow the same approach as outlined for clonidine.

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $p<0.05$.

Analyses of secondary and tertiary efficacy parameters

The first occurrence of the secondary composite outcomes will be analyzed up to 30 days after randomization using the same analytical approach as for the primary efficacy variable. The first occurrence of each individual tertiary outcome will be analyzed at 30 days after randomization using the same analytical approach as for the primary efficacy variable except for 2 outcomes (i.e., length of hospital stay, and length of ICU/CCU stay), which will be analyzed using a Student's t test. For patients who die in-hospital during their index hospitalization, the last day of hospital admission will be the date the patient dies.

Primary subgroup analyses on the secondary efficacy parameter

We will undertake one subgroup analysis for our secondary outcome of the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis. Cox proportional hazards models assessing this secondary outcome will provide the basis for evaluating the

following ASA subgroup analysis: ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum).

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $p<0.05$.

Safety analysis

We will tabulate the number of safety outcomes by treatment group at 30 days after randomization. We will compare the rate of occurrence of each safety outcome using the same analytical approach as for the primary efficacy variable.

Adverse events will be coded and analyzed using MedDRA®.

Appendix: Outcome definitions

Outcome	Definition
Sub classification of death	Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).
Myocardial infarction	The diagnosis of myocardial infarction requires any one of the following criterion: 1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also requires that 1 of the following must also exist: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; C. ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. coronary artery intervention (i.e., PCI or CABG surgery); or E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; 2. Pathologic findings of an acute or healing myocardial infarction; or 3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.

Nonfatal cardiac arrest	Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Cardiac revascularization procedure	Cardiac revascularization procedure is defined as PCI or CABG surgery.
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.
Pulmonary embolism	The diagnosis of pulmonary embolism requires any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan; or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan.
Deep venous thrombosis of leg or arm	The diagnosis of deep venous thrombosis requires any one of the following: 1. A persistent intraluminal filling defect on contrast venography; 2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or 3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.
New clinically important atrial fibrillation	New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Re-hospitalization for vascular reasons	Re-hospitalization for vascular reasons is defined as re-hospitalization for myocardial infarction, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolus, any vascular surgery, or bleeding.

Life-threatening bleeding	Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" above, and results in any one of the following: 1. a hemoglobin ≤70 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 2. a hemoglobin drop of ≥50 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 3. the patient receives a transfusion of ≥4 units of red blood cells within a 24 hour period; 4. any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or 5. retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.
Clinically important hypotension	Clinically important hypotension is defined as a systolic blood pressure <90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.
Clinically important bradycardia	Clinically important bradycardia is defined as a heart rate <55 beats per minute requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.
Congestive heart failure	The definition of congestive heart failure requires at least one of the following clinical signs (i.e., any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
New acute renal failure requiring dialysis	Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.
Amputation	Amputation is defined as an amputation procedure subsequent to the initial surgery.

Peripheral arterial thrombosis	We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis: 1. Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism; 2. Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism; 3. Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism; or 4. Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism.
Infection	Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.
Sepsis	Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature >38^{o}C or <36^{o}C; heart rate >90 beats per minute; respiratory rate >20 breaths/minute; white blood cell count >12 x 10^{9}/L or <4 x 10^{9}L.

PeriOperative ISchemic Evaluation-2 (POISE-2) Trial

SHORT-TERM STATISTICAL ANALYSIS PLAN

POPULATION HEALTH RESEARCH INSTITUTE

11:45 PM, January 24, 2014

1. TRIAL OBJECTIVES

Primary Efficacy Objective:

1. To determine the impact of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of mortality or nonfatal myocardial infarction (MI) in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.

Secondary Efficacy Objectives:

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of mortality, nonfatal MI, and nonfatal stroke up to 30 days after randomization.

2. To determine among all the ASA patients the impact on a composite outcome of mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis up to 30 days after randomization and whether the effects differ from each other in each ASA stratum.

Tertiary Efficacy Objectives:

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual tertiary outcomes up to 30 days after randomization: mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary embolism, deep venous thrombosis, new clinically important atrial fibrillation, amputation, peripheral arterial thrombosis,

infection, sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

Safety Objectives:

1. To determine the impact of perioperative low-dose clonidine on each of the following individual outcomes up to 30 days after randomization: stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure.
2. To determine the impact of perioperative low-dose ASA on each of the following individual outcomes up to 30 days after randomization: stroke, clinically important hypotension, congestive heart failure, life-threatening bleeding, and major bleeding.

2. TRIAL OUTCOME EVENTS

Primary Efficacy Outcome for Clonidine and ASA

1. The primary efficacy outcome is the first occurrence of any component of the following composite up to day 30 after randomization: mortality or nonfatal MI.

Secondary Efficacy Outcomes

1. A secondary efficacy outcome for clonidine and ASA is the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, or nonfatal stroke.

2. A secondary efficacy outcome among all the ASA patients and whether the effects differ in each of the two ASA strata on the outcome of the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis.

Tertiary Efficacy Outcomes up to 30 Days after Randomization for Clonidine and ASA

1. Mortality
2. Vascular mortality
3. MI
4. Nonfatal cardiac arrest
5. Cardiac revascularization procedure
6. Pulmonary embolism
7. Deep venous thrombosis
8. New clinically important atrial fibrillation
9. Amputation
10. Peripheral arterial thrombosis
11. Infection
12. Sepsis
13. Rehospitalization for vascular reasons
14. Length of hospital stay
15. Length of intensive care unit / cardiac care unit (ICU/CCU) stay

16. New acute renal failure requiring dialysis

Safety Outcomes up to 30 Days after Randomization for Clonidine

1. Stroke
2. Clinically important hypotension
3. Clinically important bradycardia
4. Congestive heart failure

Safety Outcomes up to 30 Days after Randomization for ASA

1. Stroke
2. Clinically important hypotension
3. Congestive heart failure
4. Life-threatening bleeding
5. Major bleeding

The definition of all the outcomes is defined in the Appendix.

3. STATISTICAL AND ANALYTICAL METHODS

Analysis population

All efficacy and safety analyses will include all randomized patients. We will analyze patients in the treatment group to which they were originally allocated. There is no intention to define a per protocol population. We will include all events that centres have reported and the adjudication committee has not refuted.

Efficacy analysis

Primary efficacy analyses

The primary efficacy variable is the first occurrence of mortality or nonfatal myocardial infarction up to 30 days after randomization. We will compare patients allocated to clonidine with patients allocated to clonidine placebo, and we will compare patients allocated to ASA with patients allocated to ASA placebo. Patients lost to follow-up before day 30 after randomization with no primary outcome event reported will be censored at the last day the patient had a complete evaluation of the primary efficacy variable.

The primary efficacy variable will be analyzed using a stratified (by the opposite component of the factorial design and ASA starting/continuing strata) Cox proportional hazards model. All follow up will be censored at day 30 or their outcome day, whichever occurs first. We will address the clonidine objective of superiority through the following hypotheses:

H_0: Hazard ratio of clonidine versus placebo (at 30 days after randomization) = 1

H_a: Hazard ratio of clonidine versus placebo (at 30 days after randomization) ≠ 1

We will consider clonidine superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

We will address the ASA objective of superiority through the following hypotheses:

H_0: Hazard ratio of ASA versus placebo (at 30 days after randomization) = 1

H_a: Hazard ratio of ASA versus placebo (at 30 days after randomization) ≠ 1

We will consider ASA superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

Estimates of the hazard ratios and two-sided 95% confidence intervals will be calculated using the Cox proportional hazards model. If the validity of the proportional hazards assumption is not acceptable, we will compare the proportion of patients with a primary outcome at 30 days after randomization between the two treatment groups, controlling for the same stratification factors. We will also summarize the primary outcome event with Kaplan-Meier curves by treatment group.

Primary subgroup analyses on the primary efficacy parameter

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following clonidine subgroup analyses: 1.neuraxial blockade versus no neuraxial blockade (i.e., we expect clonidine to have a greater beneficial effect in patients who did not receive neuraxial blockade compared to patients who did receive neuraxial blockade); 2. vascular surgery versus no vascular surgery (i.e., we expect clonidine to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); 3. beta-blocker usage in the 24 hours preceding surgery versus no beta-blocker usage in the 24 hours preceding surgery (we expect clonidine to have a greater beneficial effect in patients who did not receive a beta-blocker in the 24 hours prior to surgery compared to patients who did receive a beta-blocker in the 24 hours before surgery) and 4. baseline risk according to number of Revised Cardiac Risk Index (RCRI) criteria (i.e., we expect clonidine to have

a greater beneficial effect in patients with more RCRI criteria compared to patients with less RCRI criteria).

For the subgroup analyses based on the number of RCRI criteria, we will examine if treatment effect varies across the number of RCRI criteria between the two treatment groups. The RCRI criteria consist of the following variables.

1. history of coronary artery disease
2. history of congestive heart failure
3. history of stroke or transient ischemic attack
4. diabetes and preoperative treatment with insulin or an oral hypoglycemic agent
5. preoperative serum creatinine >175 μmol/L [>2.0 mg/dl]
6. high-risk surgery defined as major vascular, major thoracic, or major general surgery

The analysis will consist, for each number of eligibility criteria (i.e., 0, 1, 2, 3, or ≥4), of a stratified Cox proportional hazards model, incorporating terms for treatment group, the individual number of RCRI criteria, and the treatment group by subgroup interaction.

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following ASA subgroup analyses: 1. ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum); 2. vascular surgery versus no vascular surgery (i.e., we expect ASA to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); and 3. baseline risk according to number of RCRI criteria (i.e., we expect ASA to have a greater beneficial effect in patients with more

RCRI criteria compared to patients with less eligibility criteria). The subgroup analyses based on the number of RCRI criteria for ASA will follow the same approach as outlined for clonidine.

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $p<0.05$.

Analyses of secondary and tertiary efficacy parameters

The first occurrence of the secondary composite outcomes will be analyzed up to 30 days after randomization using the same analytical approach as for the primary efficacy variable. The first occurrence of each individual tertiary outcome will be analyzed at 30 days after randomization using the same analytical approach as for the primary efficacy variable. For new acute renal failure requiring dialysis we did not collect the date that dialysis was initiated after randomization, and we will therefore use a log-rank tests. For length of hospital stay and length of ICU/CCU stay we will use log-rank tests and censor those who remain in hospital greater than 30 days. For patients who die in-hospital within 30 days of randomization and during their index hospitalization, their follow up will be censored on the date of death.

Primary subgroup analyses on the secondary efficacy parameter

We will undertake one subgroup analysis for our secondary outcome of the first occurrence of any component of the following composite up to day 30 after

randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis. Cox proportional hazards models assessing this secondary outcome will provide the basis for evaluating the following ASA subgroup analysis: ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum). For this subgroup analysis, we will remove the ASA continuation/starting factor as a strata within the Cox regression.

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $p<0.05$.

Safety analysis

We will tabulate the number of safety outcomes by treatment group at 30 days after randomization. We will compare the rate of occurrence of each safety outcome using the same analytical approach as for the primary efficacy variable.

Adverse events will be coded and analyzed using MedDRA®.

Appendix: Outcome definitions

Outcome	Definition
Sub classification of death	Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy).
Myocardial infarction	The diagnosis of myocardial infarction requires any one of the following criterion: 1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also requires that 1 of the following must also exist: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; C. ECG changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. coronary artery intervention (i.e., PCI or CABG surgery); or E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; 2. Pathologic findings of an acute or healing myocardial infarction; or 3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event.

Nonfatal cardiac arrest	Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Cardiac revascularization procedure	Cardiac revascularization procedure is defined as PCI or CABG surgery.
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.
Pulmonary embolism	The diagnosis of pulmonary embolism requires any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan; or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan.
Deep venous thrombosis of leg or arm	The diagnosis of deep venous thrombosis requires any one of the following: 1. A persistent intraluminal filling defect on contrast venography; 2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or 3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.
New clinically important atrial fibrillation	New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Re-hospitalization for vascular reasons	Re-hospitalization for vascular reasons is defined as re-hospitalization for myocardial infarction, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolus, any vascular surgery, or bleeding.

Life-threatening bleeding	Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" above, and results in any one of the following: 1. a hemoglobin ≤70 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 2. a hemoglobin drop of ≥50 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 3. the patient receives a transfusion of ≥4 units of red blood cells within a 24 hour period; 4. any one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); or 5. retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.
Clinically important hypotension	Clinically important hypotension is defined as a systolic blood pressure <90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.
Clinically important bradycardia	Clinically important bradycardia is defined as a heart rate <55 beats per minute requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.
Congestive heart failure	The definition of congestive heart failure requires at least one of the following clinical signs (i.e., any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
New acute renal failure requiring dialysis	Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.
Amputation	Amputation is defined as an amputation procedure subsequent to the initial surgery.

Peripheral arterial thrombosis	We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we require at least one of the following objective findings of peripheral arterial thrombosis: 1. Surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism; 2. Pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism; 3. Imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism; or 4. Autopsy reports documenting arterial thrombosis/ peripheral arterial embolism.
Infection	Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.
Sepsis	Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature >38^{o}C or <36^{o}C; heart rate >90 beats per minute; respiratory rate >20 breaths/minute; white blood cell count >12 x 10^{9}/L or <4 x 10^{9}L.

POISE-2 Statistical Analysis Plan Changes (11:45 PM, January 24, 2013)

Bold font indicates the changes.

Tertiary Efficacy Objectives:
There were two typographical errors in this section. One error was in describing these outcomes as secondary outcomes in the text of this section on tertiary outcomes. The second was in not appropriately characterizing the outcome of clinically important atrial fibrillation as new clinically important atrial fibrillation. Therefore this section was updated:

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual **tertiary** outcomes mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary embolism, deep venous thrombosis, **new** clinically important atrial fibrillation, amputation, peripheral arterial thrombosis, infection, sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

Primary efficacy analyses:
The variables used in the stratified Cox proportional hazards model were updated to include all the variables. In this section we also clarified that all follow-up was to be censored at day 30 or the outcome day, whichever occurred first. Finally in the section, we removed the following statement because our primary analyses were based upon the Cox proportional hazards models. "We will use log-rank tests to compare the rate of occurrence of the primary outcome between the ASA versus the ASA placebo group and separately the clonidine versus the clonidine placebo group."

The primary efficacy variable will be analyzed using a stratified (**by the opposite component of the factorial design and ASA starting/continuing strata**) Cox proportional hazards model. **All follow up will be censored at day 30 or their outcome day, whichever occurs first.**

Primary subgroup analyses on the primary efficacy parameter:
Based upon reviewers' comments during the review process of the POISE-2 Methods paper (Am Heart J 2014;doi: 10.1016/j.ahj.2014.01.007.), we decided to add a clonidine subgroup analysis based upon whether a patient received a beta-blocker in the 24 hours preceding surgery and an aspirin subgroup analysis based upon whether the patient underwent vascular surgery. Originally we were undertaking a subgroup analysis for both clonidine and aspirin based on the baseline risk according to number of eligibility criteria; however, based upon reviewers' comments we changed this to the baseline risk according to number of Revised Cardiac Risk Index (RCRI) criteria.

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following clonidine subgroup analyses: 1.neuraxial blockade versus no neuraxial

blockade (i.e., we expect clonidine to have a greater beneficial effect in patients who did not receive neuraxial blockade compared to patients who did receive neuraxial blockade); 2. vascular surgery versus no vascular surgery (i.e., we expect clonidine to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); **3. beta-blocker usage in the 24 hours preceding surgery versus no beta-blocker usage in the 24 hours preceding surgery (we expect clonidine to have a greater beneficial effect in patients who did not receive a beta-blocker in the 24 hours prior to surgery compared to patients who did receive a beta-blocker in the 24 hours before surgery) and 4. baseline risk according to number of Revised Cardiac Risk Index (RCRI) criteria (i.e., we expect clonidine to have a greater beneficial effect in patients with more RCRI criteria compared to patients with less RCRI criteria).**

For the subgroup analyses based on the number of RCRI criteria, we will examine if treatment effect varies across the number of RCRI criteria between the two treatment groups. The RCRI criteria consist of the following variables.

1. history of coronary artery disease
2. history of congestive heart failure
3. history of stroke or transient ischemic attack
4. diabetes and preoperative treatment with insulin or an oral hypoglycemic agent
5. preoperative serum creatinine >175 μmol/L [>2.0 mg/dl]
6. high-risk surgery defined as major vascular, major thoracic, or major general surgery

The analysis will consist, for each number of eligibility criteria (i.e., 0, 1, 2, 3, or ≥4), of a stratified Cox proportional hazards model, incorporating terms for treatment group, the individual number of RCRI criteria, and the treatment group by subgroup interaction.

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following ASA subgroup analyses: 1. ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum); **2. vascular surgery versus no vascular surgery (i.e., we expect ASA to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); and 3. baseline risk according to number of RCRI criteria (i.e., we expect ASA to have a greater beneficial effect in patients with more RCRI criteria compared to patients with less eligibility criteria). The subgroup analyses based on the number of RCRI criteria for ASA will follow the same approach as outlined for clonidine.**

<u>Analyses of secondary and tertiary efficacy parameters</u>:
Because we did not collect the time when dialysis was initiated after surgery we corrected the analytic approach. We also updated the analytic approach for the length of stay outcomes, and we clarified the timing of censoring.

The first occurrence of the secondary composite outcomes will be analyzed up to 30 days after randomization using the same analytical approach as for the primary efficacy variable. The first occurrence of each individual tertiary outcome will be analyzed at 30 days after randomization using the same analytical approach as for the primary efficacy variable. **For new acute renal failure requiring dialysis we did not collect the date that dialysis was initiated after randomization, and we will therefore use a log-rank tests. For length of hospital stay and**

length of ICU/CCU stay we will use log-rank tests and censor those who remain in hospital greater than 30 days. For patients who die in-hospital within 30 days of randomization and during their index hospitalization, their follow up will be censored on the date of death.

Primary subgroup analyses on the secondary efficacy parameter:
In this section we clarified that we had to remove the ASA continuation/starting factor as a strata within the Cox regression.

We will undertake one subgroup analysis for our secondary outcome of the first occurrence of any component of the following composite up to day 30 after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis. Cox proportional hazards models assessing this secondary outcome will provide the basis for evaluating the following ASA subgroup analysis: ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum). **For this subgroup analysis, we will remove the ASA continuation/starting factor as a strata within the Cox regression.**